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PRIMARY IRON-DEFICIENCY ANAEMIA IN YOUNG MEN[1]

By W. BRUMFITT

(From St. Mary's Hospital, London, and the
Cambridge Military Hospital, Aldershot)

It is widely held that iron-deficiency anaemia, not associated with organic disease, is rare in adolescent or adult male subjects (Sturgis, 1955; Wintrobe, 1956; Whitby and Britton, 1957). In his original description of 'achylia gastrica with anaemia' Faber (1909) noted that the condition was uncommon in men, and repeated this opinion in subsequent publications (Faber, 1913; Faber and Gram, 1924). Nolan (1925) described two male patients, aged 16 and 18 years, in a series of 19 cases. These two youths showed features of infantilism, and both had achlorhydria. Gardiner-Hill (1931) and Filo (1933) each described similar cases. Witts (1930*a*) reported 50 cases of 'simple achlorhydric anaemia', of which only one occurred in a male subject. Discussing the difference in sex incidence, he remarked that the disparity was not so great as his figures suggested. In the Appendix to his paper he described six other male patients, originally excluded because each had a lesion which might have caused the anaemia. In the same year Witts (1930*b*) described five cases in male patients, in whom no cause for the anaemia could be found. The oldest of these patients was 28, and the term 'late chlorosis' was used to describe the anaemia. Subsequently Witts and Berger (1934) described 26 cases in male patients; eight were under 30 years of age; all showed a tendency to immaturity, and no cause for the anaemia could be detected.

In the present paper the term *primary* iron-deficiency anaemia will be reserved for those patients in whom an exhaustive search for an underlying cause has been made but none found. Some patients have been described in other reports as suffering from idiopathic iron-deficiency anaemia, although conditions such as occult bleeding and steatorrhoea had not been excluded. It is convenient to retain the term *idiopathic* iron-deficiency anaemia to describe cases in which no cause for the anaemia was found, but where the scope of the investigations was insufficient to justify a diagnosis of primary iron-deficiency anaemia. Cases of idiopathic iron-deficiency anaemia in male patients have been reported by Davies (1931*a*, *b*), Dameshek (1931), Adamson and Smith (1931), Weber and Weisswange (1933), and Wintrobe and Beebe (1933). All these authors emphasized the rarity of the condition in men. Forshaw (1954) examined the records of three large hospitals over a period of four years, and was able to find only 11 male patients suffering from primary iron-deficiency

[1] Received February 23, 1959.

anaemia. There are, however, a few reports of iron-deficiency anaemia in young male recruits to the armed forces. Thomson (1943) described 10 male patients with iron-deficiency anaemia, in whom he could find no evidence of haemorrhage. All but one were aged 17 to 20. These men were leading a normal life, and none had a significant past history. Shorthouse and King (1951) reported 20 cases from a military hospital where men of all ages were treated. Their oldest patient was 23, and the remainder under 20 years of age. Leonard (1954)

TABLE I

Results of Haemoglobin Estimations in Young Men

	Present investigation			*M.R.C. survey (1945)*	
Haemoglobin (%)*	*2,000 R.A.M.C. recruits* (%)		*1,000 trained soldiers of the Airborne Regiment* (%)		*489 married and single men under 20 years old* (%)
30–	..		..	..	
35–	..		..	..	
40–	..		..	..	
45–	..		..	0·2	
50–	0·05		..	..	
55–	..		..	..	
60–	0·1		..	..	1·8
65–	0·15	1·1	..	..	
70–	0·2		..	0·4	
75–	0·6		0·1	1·2	
80–	1·3		0·4	2·0	
85–	2·3		1·6	5·5	
90–	10·2	37·9	8·1	10·3	39·1
95–	24·1		25·0	21·3	
100–	28·5		26·4	..	
105–	18·0		20·8	..	
110–	11·2	61·0	12·4	..	58·1
115–	2·3		3·8	..	
120–	1·0		1·2	..	
125 and over	..		0·2	..	

* 100 per cent. = 14·8 g. per 100 ml.

examined the haemoglobin levels of 4,221 Royal Air Force recruits, using the copper sulphate method as a screening test to detect anaemia, which he defined as a haemoglobin level below 11·8 g. per 100 ml. (80 per cent.). Fifty men were found to be anaemic, and in 47 no primary organic cause was discovered. In the present work the incidence of anaemia has been determined in 2,000 recruits to the Royal Army Medical Corps. For comparison, estimations were made on 1,000 men of the Airborne Regiment who had recently completed their training and might reasonably be assumed to be extremely healthy. Recruits who were found to be anaemic during this survey, in addition to other soldiers thought to be suffering from iron-deficiency anaemia, were admitted to hospital for investigation. After exhaustive studies had been made, there remained a group of 30 anaemic patients in whom no organic disease was found. The response of these patients to treatment with iron was observed in hospital, and follow-up examination after an interval of three to 12 months was possible in 29 cases.

Incidence of Anaemia in Recruits to the Royal Army Medical Corps

Haemoglobinometry was carried out photoelectrically, and calibration of the pipettes checked by the method of Stevenson, Smetters, and Cooper (1951). In view of the diurnal variation in haemoglobin levels (McCarthy and Van Slyke, 1939; Brown and Goodall, 1946), blood for haemoglobin estimation was taken between 10 and 11.30 a.m. A haemoglobin level of 11·8 g. per 100 ml. (80 per cent.) was arbitrarily chosen as the lower limit of normal. Of the 2,000

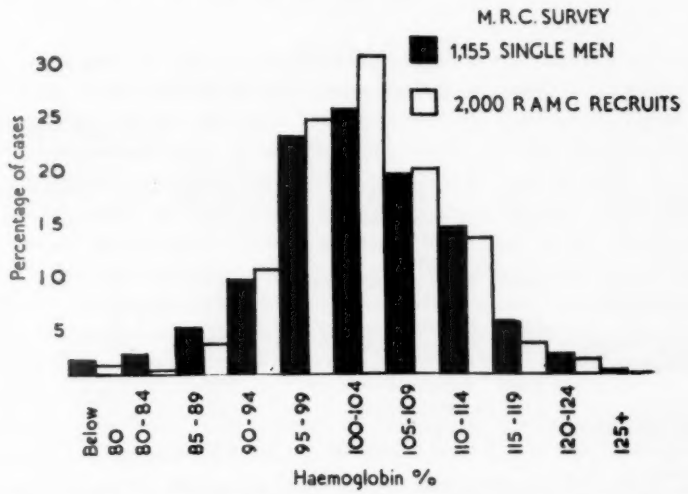

FIG. 1. The incidence of anaemia in 2,000 Royal Army Medical Corps recruits compared with the Medical Research Council Survey (1945) of healthy men under 20 years of age.

recruits examined, the blood in 22 fell below this level (Table I). In Fig. 1 the haemoglobin levels found by the Medical Research Council survey (1945) in healthy men under 20 years of age are compared with those found in the present investigation, and a striking similarity in distribution is seen. For comparison with the Royal Army Medical Corps recruits, estimations were made on 1,000 trained men of the Airborne Regiment, and it was found that only one man had a haemoglobin level of less than 11·8 g. per 100 ml. (Table I).

A higher incidence of anaemia in recruits compared with trained soldiers has recently been shown in small groups by Stewart, Yeates, and Barnfather (1957). They found two cases of anaemia in a group of 140 recruits (1·4 per cent.), but there were no cases among 89 soldiers at a Guards Depot where all the men had completed their training. The criterion of anaemia was the same as in the present survey. It is interesting that the large series of Royal Air Force recruits investigated by Leonard (1954), a group which can be taken to be exactly comparable with that described here, showed an almost identical incidence of anaemia. It may be concluded that primary iron deficiency anaemia of male

subjects occurs in rather more than one per cent. of recruits to the armed forces. Anaemia is, therefore, more common in service recruits than in soldiers such as those of the Airborne Regiment who have completed a training programme requiring a high standard of physical fitness. The Airborne group is, of course, highly selected, since any soldier unable to complete the rigorous training would be excluded. The inference is that the anaemia precludes the completion of a hard course of training, even though the sufferers claim to be symptomless. The only alternative explanation is that spontaneous resolution of the anaemia takes place after a short period of army service.

TABLE II

Surveys of Haemoglobin Levels in Men

Investigator	*Year*	*Status*	*Number examined*	*Percentage with haemoglobin below 12 g./100 ml.*	*Age (years)*
Price-Jones	1931	Medical students and laboratory staff	100	0	Average 27
Wintrobe	1933	American students	86	0	..
Jenkins and Don	1933	British	118	0	..
Walters	1934	American	100	0	20–30
Price-Jones, Vaughan, and Goddard	1935	Medical students	90	0	20–42
Osgood	1935	American	259	0	14–30+
Hamré and Ao	1942	Cosmopolitan	137	0·7	16–25
Davidson, Donaldson, Lindsay, and MacSorley	1943	Students	100	0	..
		Factory workers	123	0·8	..
M.R.C. Special Report	1945	British	489	1·8	Under 20
			1,115	1·5	All ages
Heath	1948	American	285	0	..
Adcock, Brown, Magee, and Milligan	1948	Soldiers and policemen	634	0	18–40+
Berry, Beveridge, Bransby, Chalmers, Needham, Magee, Townsend, and Daubney	1949	Olympic athletes	147	0	16–47
Leonard	1954	R.A.F. recruits	4,221	1·2	17–21
Stewart, Yeates, and Barnfather	1957	Recruits at Guards Depot	140	1·4	17–22
		Trained soldiers	89	0	18–24
Present investigation	1954–56	R.A.M.C. recruits	2,000	1·1	17–21
		Trained men of Airborne Regiment	1,000	0·1	18–26

It is seen from Table II that before 1942 investigators found no anaemia in the groups of male subjects which they examined. The individual groups are small, but taken as a whole they would be expected to show an occasional anaemic patient if such patients occurred. In all these studies the average age of the group was higher than in the present series. The absence of the illness in older age groups raises the important possibility that this form of anaemia occurs only in young men and is a self-limiting condition.

Investigation of 30 Male Patients with Primary Iron-deficiency Anaemia

Exclusion of an organic cause for the anaemia

The present cases were derived from a larger series of anaemic patients after clinical and laboratory studies had failed to reveal an organic basis for the anaemia. The anaemic patients investigated included the recruits found to be anaemic in the survey already described, in addition to other soldiers referred to hospital because they were thought to be suffering from iron deficiency anaemia. Particular attention was paid to the exclusion of the following:

1. *Loss of blood.* There is a considerable weight of opinion in support of the view that iron-deficiency anaemia in the adult is a very rare condition unless accompanied by chronic bleeding (see, for example, Heath and Patek, 1937; Moore, 1950, 1955; Sturgis, 1955; Wintrobe, 1956). In the present cases there was no clinical evidence to suggest a lesion of the alimentary tract, and radiological examination of the stomach and intestine, including examination for hiatus hernia, was negative. Tests for faecal occult blood were also repeatedly negative. Oral iron was given, in doses of approximately 150 mg. of bivalent iron daily, until the anaemia was corrected. Although the patients were given no further treatment and followed up for periods of up to one year, in no instance did relapse occur. If there were chronic bleeding, relapse would be expected in a proportion of cases.

2. *Chronic diarrhoea.* The association between hypochromic anaemia and disorders of the alimentary tract, such as chronic diarrhoea (Keefer, Huang, and Yang, 1929) and idiopathic steatorrhoea (Bennett, Hunter, and Vaughan, 1932; Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946; Badenoch and Callender, 1954), is well established. None of the present patients gave a history of loss of weight or diarrhoea, but because such symptoms may be absent in idiopathic steatorrhoea (Cooke, 1952) further investigation of all patients was considered necessary. Barium-meal and follow-through examinations, fat-balance tests, glucose-tolerance tests, and iron-absorption tests were all normal. The haematological features characteristic of idiopathic steatorrhoea (Cooke, Frazer, Peeney, Sammons, and Thompson, 1948) were absent. In addition, all patients responded well to small doses of oral iron.

3. *Infection.* Anaemia may be found in association with a variety of chronic infections, in the absence of blood loss and without obvious haemolysis. The anaemia is usually normocytic and normochromic, but may occasionally be hypochromic or microcytic (Saifi and Vaughan, 1944; Cartwright and Wintrobe, 1955). No patient gave a history of chronic illness, and the white-cell count, erythrocyte sedimentation rate, chest X-rays, and urine examination were normal. The iron-absorption test invariably showed a normal or better than normal uptake of iron after two hours, whereas in the anaemia of chronic infection there is little or no rise above the fasting level (Cartwright, Lauritsen, Jones, Merrill, and Wintrobe, 1946; Jasinski, 1949).

Clinical Study of Primary Iron-deficiency Anaemia

Symptoms. Although patients whose ages ranged from 16 to 60 years were seen at the hospital, all the patients in the present series were aged 18 or 19, and with one exception had been in the army for less than three months. The

TABLE III

Signs in 30 Cases of Primary Iron-deficiency Anaemia

	Number of cases		*Number of cases*
Pallor:		Mouth:	
Skin	12	Glossitis	1
Conjunctivae	21	Smooth tongue	6
Gums	19	Cheilosis	0
Nail beds	12	Bleeding gums	0
Skin creases of hand	0		
Nails:		Heart:	
Koilonychia	2	Systolic murmur	14
Flattened	2	Diastolic murmur	0
Cracked distally	7	Cardiac enlargement	0
		Spleen:	
		Enlargement	1

TABLE IV

Primary Iron-deficiency Anaemia compared with the Iron-deficiency Anaemia of Middle-aged Women and of Pregnancy

		Number of cases	*Dyspnoea on effort*	*Alimentary symptoms*	*Tongue*		*Pallor*	*Nail changes*		*Spleen*	*Cardiac systolic murmur*
					Smooth	*Sore*		*Koilonychia*	*Other abnormalities*		
Middle-aged women	Witts (1930a)	49	78%	52%	50%	20%	Often absent	8%	ND	32%	ND
	Wintrobe and Beebe (1933)	Review of 260	Very common	56%	28%	Infrequent	Striking and common	Infrequent	64%	50%	Very common
Iron deficiency of pregnancy	Gatenby and Lillie (1955)	397	66%	10% (excluding vomiting)	ND	1·5%	See note*	3%	7%	ND	ND
Young men	Thomson (1943)	10	Slight in a few cases	0	40%	0	Very common	40%	0	40%	Nearly all
	Shorthouse and King (1951)	20	75%	15%	0	0	Very common	20%	15%	20%	20%
	Leonard (1954)	47	Uncommon; slight when present	0	38%	0	28%	2%	21%	4%	ND
	Present series	30	50%	0	30%	3%	39%	6%	29%	3%	46%

ND = no data given.

* Obvious pallor of skin or conjunctivae in 54·5 per cent. (separate figures for skin pallor not given).

insidious onset, and vague symptoms such as tiredness and weakness, make diagnosis difficult, and add to the danger of the patient being labelled as a malingerer or a hysteric. The ultimate relation of all the symptoms to lack of iron was shown by their disappearance after iron had corrected the anaemia. The symptoms could be grouped under two major headings, shortness of breath

and lack of energy. The former symptom was complained of spontaneously by nine of the 30 patients, and when the remaining patients were questioned about their exercise tolerance it became obvious that dyspnoea on effort was present in a further six. Three patients with haemoglobin levels below 7·4 g. per 100 ml. made no spontaneous complaint of breathlessness; one denied having any symptoms at all, and was able to play a game of football without distress. There was nevertheless a relationship between the severity of the anaemia and dyspnoea on effort, which was present in 11 of the 13 patients with haemoglobin values below 8·9 g. per 100 ml., but in none of the eight patients with a haemoglobin value greater than 9·6 g. per 100 ml. No patient complained of dysphagia, anorexia, flatulence, or diarrhoea, but one had suffered from periodic sore tongue during the previous three years.

TABLE V

Social Background of Men with Primary Iron-deficiency Anaemia

Social class	*Present series*	*Leonard (1954)*
I	0	0
II	2	0
III	11	2
IV	5	8
V	7	24
Father unemployed	1	7
,, deceased	4	6
Total	30	47

In Table IV the findings in primary iron-deficiency anaemia of young men are compared with those of idiopathic iron-deficiency anaemia of middle-aged women (Witts, 1930*a*; Wintrobe and Beebe, 1933), and with those of iron-deficiency anaemia of pregnancy (Gatenby and Lillie, 1955). Middle-aged women with a comparable degree of anaemia more commonly complain of breathlessness on effort, probably because they are more often obese, and their cardio-respiratory systems are on the whole less efficient than those of the young men. A further difference is the virtual absence in the young men of alimentary symptoms such as dysphagia, dyspepsia, or diarrhoea. The higher incidence of dysphagia in women may be related to the longer duration of the disease, since the average duration of symptoms in women is eight years (Wintrobe, 1956), whereas in the present series the average duration of symptoms was 1·8 years. The difference in other alimentary symptoms is more difficult to explain, but abdominal symptoms are so uncommon in the young men that when they are present an alimentary lesion should be suspected.

Diet. Special attention was paid to appetite and to the composition of the diet, with particular regard to foods known to be rich in iron. In the majority of cases the appetite was good and the diet satisfactory. Four patients disliked green vegetables, and two disliked meat.

Signs. The signs are summarized in Table III. Facial pallor was found in only 39 per cent. of the patients, and was an unreliable method of diagnosing the anaemia. Leonard (1954) found an even lower figure of 28 per cent. Examina-

tion of the conjunctivae was found to be reliable when the haemoglobin was less than 10 g. per 100 ml. Berry and Cowin (1950) claimed that the colour of the gums is an unsatisfactory index of the haemoglobin level, but in the present series it correlated well with the colour of the conjunctivae. No patient had pallor of the palmar skin creases. Neither the present patients nor those of Leonard (1954) showed the tendency to immaturity which was reported by Witts and Berger (1934) and Shorthouse and King (1951).

Social background. The patients were all young men who, until joining the army, had lived at home, and more information about the social background can be gained from the occupation of the father than from the occupation of the recruit before enlistment. The father's occupation is listed according to the Registrar General's classification, and the findings of Leonard (1954) are given for comparison (Table V). The present findings differ from those of Leonard (1954) in that they do not show the same proportion of fathers falling into social class V. In only one instance was there real financial hardship and reason to believe that the family was thereby deprived of adequate food.

Anaemia in other members of the family. In view of the suggestion that relatives of patients with idiopathic hypochromic anaemia may show an unusually high incidence of anaemia (Maclachlan and Kline, 1926; Witts, 1930*a*; Heath, 1932; Lundholm, 1939), inquiries about anaemia in other relatives were made both to the patient and by letter to the family doctor. Evidence was obtained that the mother of one patient had suffered from iron-deficiency anaemia. The mother of another patient had been treated with iron for pallor, although in this case no haematological confirmation was available.

Geographical distribution. The majority of patients came from the North and the Midlands and, apart from the London area, none came from the South. Recruits report at Aldershot from all parts of Great Britain.

Laboratory Investigation

Peripheral blood. The findings are summarized in Table VI. In the stained film the most striking finding was hypochromia of the red cells, but microcytosis was not a prominent feature. The reticulocyte count was invariably less than 1 per cent., and the erythrocyte sedimentation rate and red-cell fragility were always normal.

The sternal bone-marrow was examined in eight patients, chosen so as to represent anaemia of varying severity. Films were spread at once and stained by the Jenner-Giemsa technique. The remainder of the material was fixed by the method of Cappell, Hutchison, and Smith (1947). A differential count was made, and the cellularity assessed by examination of paraffin sections stained with haematoxylin and eosin as described by Davidson, Leslie, and White (1948). Sections of marrow were also stained for iron by the method of Hutchison (1953). The findings are summarized in Table VII. Stainable iron was invariably absent, but increased cellularity of the marrow was found only in the four patients with more severe anaemia. Even in the most severe case the

myeloid: erythroid ratio was greater than unity. No support was found for the statement that normoblasts comprise 50 per cent. or more of the total nucleated cell count (Whitby and Britton, 1957). These findings are in accord with Leitner's (1949) view that only moderate hyperplasia is found in iron-deficiency

TABLE VI

Findings in the Peripheral Blood of 30 Patients with Iron-deficiency Anaemia

Case number	Haemoglobin		Packed-cell volume (%)	Red cells (millions/cu. mm.)	Mean corpuscular haemoglobin concentration (%)	Mean corpuscular volume (cu. μ)	Erythrocyte sedimentation rate (mm./1 hr.)	White cells/cu. mm.
	g./100 ml.	% *						
1	6·4	43	30	4·0	21	75	5	7,400
2	6·7	45	33	4·2	20	79	4	9,600
3	7·1	48	32	3·8	22	84	6	5·600
4	7·4	50	32	4·4	24	75	6	8,700
5	7·4	50	33	4·5	22	73	6	9,600
6	7·7	52	34	4·6	23	74	3	9,200
7	8·0	54	34	4·3	23	77	3	8,100
8	8·0	54	32	4·8	26	67	2	8,600
9	8·1	55	32	3·9	25	82	4	7,400
10	8·4	57	35	4·5	24	77	2	5,600
11	8·6	58	34	4·0	25	85	3	6,900
12	8·6	58	37	4·2	23	88	2	8,500
13	8·6	58	36	4·6	24	78	3	5,700
14	8·9	60	36	4·8	25	75	2	8,900
15	8·9	60	36	4·4	25	82	3	8,700
16	8·9	60	35	4·3	25	81	3	4,760
17	8·9	60	39	4·3	23	91	5	8,100
18	8·9	60	34	4·6	26	73	2	9,200
19	9·2	62	35	5·2	26	69	4	6,300
20	9·5	64	40	4·9	24	82	3	7,400
21	9·5	64	37	4·4	26	84	1	8,900
22	9·5	64	37	4·4	26	84	2	6,100
23	9·8	66	39	4·5	26	86	3	8,800
24	9·8	66	42	4·7	23	89	2	8,400
25	10·0	67	40	4·3	25	93	1	6,200
26	10·2	69	38	4·4	27	86	2	5,900
27	10·4	70	36	4·7	29	76	2	6,600
28	11·0	74	42	5·0	26	84	2	9,700
29	11·0	74	39	5·0	28	78	1	5,700
30	11·1	75	39	4·9	29	79	1	7,100

* 100% = 14·8 g. per 100 ml.

anaemia. It may be concluded that examination for stainable iron and qualitative assessment of the marrow are of value for diagnosis. It is doubtful whether the additional information obtained from a differential count justifies this time-consuming procedure.

The serum iron and serum iron-binding capacity. The fasting serum-iron level was estimated in every patient by the method of Dahl (1948), and was always found to be low (Table VIII). Two hours after an oral dose of 69 mg. elemental iron the rise was invariably in excess of 300 per cent. The unsaturated serum iron-binding capacity, estimated by the method of Rath and Finch (1949),

exceeded 300 μg. per ml. in every case. Ten normal control subjects all had levels below 300 μg. (Table VIII). There was no correlation between the severity of the anaemia, on the one hand, and the fasting serum iron, iron absorption, and unsaturated serum iron-binding capacity on the other.

Assessment of the iron stores. It can be seen from Table VIII that after oral iron the serum-iron levels in the iron-deficient and in the control group overlap. The range in the normal subjects was 134 to 203 μg. per 100 ml., and in the iron-deficient patients 174 to 320 μg. per 100 ml. If, however, the increase in serum iron is calculated in relation to the fasting level, a difference is immediately

TABLE VII

Results of Sternal Marrow Examination in Eight Patients with Primary Iron-deficiency Anaemia

	Peripheral blood		*Bone marrow*		
Case number	*Haemoglobin (g./100 ml.)*	*White cells per cu. mm.*	*Myeloid:erythroid ratio*	*Stainable iron*	*Marrow report*
1	6·4	7,400	1·48:1	Nil	Hyperplastic marrow involving the normoblast series
7	8·0	8,100	1·4 :1	,,	
8	8·0	8,600	1·9 :1	,,	
10	8·4	5,600	1·6 :1	,,	
11	8·6	6,900	2·5 :1	,,	Cellularity within normal limits, but slight increase in normoblast series
15	8·9	8,700	2·9 :1	,,	
26	10·2	5,900	2·3 :1	,,	
29	11·0	5,700	3·1 :1	,,	

TABLE VIII

The Results of the Iron-Absorption Test and the Serum Unsaturated Iron-Binding Capacity in the Patients compared with 10 Normal Men (all aged 18)

		Serum iron (μg./100 ml.)		*Increase over fasting level*		*Serum unsaturated iron binding capacity (μg./100 ml.)*
		Fasting	*2 hrs. after 69 mg. iron*	*μg./100 ml.*	*%*	
30 patients with iron deficiency anaemia	Average	34	199	165	485	400
	Range	23–45	174–320	132–297	316–1,300	320–490
10 normal men	Average	115	157	42	37	210
	Range	98–160	134–203	30–87	19–80	194–275

apparent. In the control group the greatest individual increase was from 110 to 203 μg. per 100 ml. (a rise of 80 per cent.), whereas the smallest individual increase in the iron-deficient patients was from 42 to 174 μg. per 100 ml. (a rise of 316 per cent.).

The present findings are in agreement with those of Verloop, Meeuwissen, and Blokhuis (1958), who also found the absorption test a reliable means of demonstrating iron deficiency. Doubts have been cast on the value of information given by the iron-absorption test (Hahn, Bale, Ross, Balfour, and Whipple, 1943; Smith, 1952; Bothwell, Mallett, Oliver, and Smith, 1955), but it is probable that the disrepute into which the test has fallen in some centres is due to the exaggerated claims and interpretations which have been placed on the

findings rather than to inadequacies of the test itself. The present investigation was carried out in a group of young men suffering from primary iron-deficiency anaemia, in whom great care had been taken to exclude other illnesses which might interfere with the test. It can be concluded that the iron-absorption test, or a combination of the fasting serum-iron and unsaturated iron-binding tests,

TABLE IX

The Individual Results Before and After Correction of the Anaemia

Case number	*Before treatment (Alcohol test meal with histamine when required)*	*Interval after treatment before follow-up*	*After treatment (Alcohol test meal with histamine when required)*
1	H.F.A.	6 months	H.F.A.
2	,,	12 ,,	Free acid
3	Acid+H	8 ,,	,,
4	Free acid	8 ,,	,,
5	H.F.A.	6 ,,	,,
6	,,	12 ,,	,,
7	,,	6 ,,	H.F.A.
8	Free acid	3 ,,	Free acid
9	H.F.A.	6 ,,	,,
10	Acid+H	12 ,,	,,
11	,,	Not followed up	..
12	H.F.A.	12 months	Free acid
13	,,	6 ,,	,,
14	Free acid	Not followed up	..
15	Acid+H*	10 months	Acid+H*
16	Free acid	6 ,,	Free acid
17	,,	12 ,,	,,
18	H.F.A.	6 ,,	H.F.A.
19	Free acid	6 ,,	Free acid
20	H.F.A.	Not followed up	..
21	Acid+H*	8 months	Acid+H
22	Free acid	9 ,,	Free acid
23	Acid+H*	6 ,,	Acid+H
24	Free acid	12 ,,	Free acid
25	H.F.A.	6 ,,	,,
26	Acid+H	12 ,,	,,
27	,,	6 ,,	,,
28	Free acid	Not followed up	..
29	,,	,, ,,	..
30	,,	,, ,,	..

H.F.A. = Histamine-fast achlorhydria.
Acid+H* = Acid only after the augmented histamine test.
Acid+H = Acid only after 0·5 mg. histamine.

can be used with confidence to demonstrate iron deficiency. The absorption test has the additional advantage of allowing the response to oral iron salts to be predicted.

The gastric secretion. The meaning of the term achlorhydria has been the subject of a recent review (Card and Sircus, 1958). The authors objected to the use of Töpfer's reagent for determination of the presence or absence of free acid in gastric secretion, on the grounds that colour change with this reagent takes place between pH 3·0 and pH 4·0, and consequently secretion of acid which does not lower the pH below this level will escape detection. In the present work all important conclusions are drawn not from single estimations, but from changes in gastric secretion before and after treatment. For example, a number

of patients had histamine-fast achlorhydria before treatment, but after correction of the anaemia free acid appeared in the gastric juice. Therefore, for present purposes, achlorhydria is defined as meaning absence of acid as detected by Töpfer's reagent. In using this definition it is appreciated that some cases labelled 'achlorhydria' may be capable of secreting acid which could be determined electrometrically. In the present series of cases the alcohol test meal with histamine (0·5 mg.) was carried out and, if no free acid was found, the test meal was repeated with the augmented histamine stimulus (Kay, 1953). It was possible to re-examine the gastric secretion in 24 of the 30 patients three to 12 months after correction of the anaemia (Table IX). From a comparison of Tables VI and IX it can be seen that there is a relationship between the severity of anaemia and the presence of histamine-fast achlorhydria. Of the 18 patients with haemoglobin levels of less than 9 g. per 100 ml., 10 (55 per cent.) had histamine-fast achlorhydria, whereas, of the 12 patients with haemoglobin levels of 9 g. or more per 100 ml., four (33 per cent.) had histamine-fast achlorhydria. Improvement in the gastric secretion of hydrochloric acid was found after treatment in 11 out of 17 cases investigated. No instance was found in which acid secretion, previously present, had disappeared at the time of follow-up.

Bennett and Ryle (1921), using the gruel test meal, found four cases of achlorhydria among 100 healthy medical students. Lander and Maclagan (1934) found an incidence of one per cent. after injection of histamine in a comparable series. Doig, Motteram, Weiden, and Wood (1950) found one case of histamine-fast achlorhydria among 134 students. Using the gastric biopsy tube, they were able to obtain gastric biopsy specimens from four students with normal secretion, and also from the student with achlorhydria. It was found that the students with acid secretion had normal mucosa. In the student with persistent histamine-fast achlorhydria there was thinning of the mucosa and atrophy of the chief and parietal cells, but no superficial inflammation. This student gave a family history of pernicious anaemia on the maternal side. Clinical examination, barium meal, and examination of the blood all gave normal results. Most authors are agreed that in iron-deficiency anaemia there is an increased incidence of achlorhydria. Witts (1956) found that under the age of 50 the incidence of achlorhydria in iron-deficiency anaemia was four times as common as in a control group. Davidson and Markson (1955) and Badenoch, Evans, and Richards (1957) investigated the gastric mucosa in iron-deficiency anaemia by use of the flexible gastric biopsy tube. Both groups of workers found a good correlation between the severity of the histological changes and the impairment of gastric secretion. The incidence of achlorhydria in the present series does not differ greatly from that found in female subjects by Davidson and Fullerton (1938), or from the various analyses carried out in young male subjects (Table X).

Of more interest, and possibly of more importance, is the effect of correction of the anaemia on the gastric secretion. Comparatively few data are available on this subject. Davidson and Fullerton (1938) suggested that histamine-fast achlorhydria might not be permanent. Hallen (1938) followed up eight patients with iron-deficiency anaemia, and reported that three to 15 months later five of

the eight were secreting hydrochloric acid. Leonard (1954) re-examined the gastric juice in 13 patients who had histamine-fast achlorhydria only six to 10 weeks after the start of treatment, at which time the haemoglobin had returned to normal. Even after this short interval he found three patients to have free acid when histamine was given. Davidson and Markson (1955) re-examined four patients with achlorhydria after treatment, and found that acid secretion returned in the two with superficial gastritis, but not in the two with atrophic gastritis. Badenoch, Evans, and Richards (1957) reported improvement in the

TABLE X

The Incidence of Achlorhydria in One Series of Female Patients (Davidson and Fullerton, 1938) and Various Series of Male Patients Suffering from Iron-deficiency Anaemia

	Number of patients	*Percentage with histamine-fast achlorhydria*	*Percentage with achlorhydria*
Davidson and Fullerton (1938)	ND	45·6	64·9
Thomson (1943)	10	ND	50
Shorthouse and King (1951)	20	ND	65
Leonard (1954)	47	43	62
Forshaw (1954)	11	54	ND
Present series	30	47*	64

ND = Data not available.
* 36 per cent. if the results of the augmented histamine test are used.

mucosa of a patient with active gastritis, as well as return of free acid, when the anaemia was cured. On the other hand, Lees and Rosenthal (1958) re-investigated 21 cases of iron-deficiency anaemia in women after treatment, and found no improvement either in the mucosa or in acid secretion. They concluded that the gastric abnormalities precede the iron deficiency and favour its development. The findings in the present series favour the view that the lesion of the gastric mucosa is secondary to the anaemia, and that the milder forms of lesion are reversible. If the achlorhydria and gastritis are fundamental in production of iron-deficiency anaemia, it is strange that the iron stores are so often adequate in pernicious anaemia. Nor is the finding that iron absorption is unimpaired after gastrectomy (Smith and Mallett, 1957; Baird, Wilson, and Podmore, 1957) easily explained.

The Aetiology of Primary Iron-deficiency Anaemia in Young Men

Since primary iron-deficiency anaemia is not of organic aetiology, it must be due to some abnormality of supply, absorption, or utilization of iron, or to excessive loss of iron. The only suggestion which has been put forward to explain primary iron deficiency in young men is that of Shorthouse and King (1951), who suggested that muscular development during the early days of army training increases the demand for iron and precipitates anaemia. Such an explanation is unlikely, since many patients were detected either before joining the army (Thomson, 1943) or, as in the present series and that of Leonard (1954),

before commencing their training. Although in the present series no evidence of haemorrhage was found in any patient, it is important to consider the aetiological significance of occult bleeding in iron-deficiency anaemia. Where investigations show an occasional weakly positive result in the test for faecal occult blood, is it justifiable to attribute the anaemia solely to haemorrhage, as suggested by Moore (1950)? Information derived from blood donors suggests that it is not. Although manifest iron-deficiency anaemia can develop in blood donors (Laurell, 1947), the work of Kaldor (1953), Davies (1953), and Hagberg, Wellenius, and Wranne (1958) indicates that it is unusual. These authors found no anaemia, and normal serum-iron values, in blood donors who had given up to 4,000 ml. of blood during the preceding year. These results indicate that the healthy individual is able to compensate for chronic loss of blood. To this consideration must be added the difficulty in interpreting an isolated weakly positive test for occult blood. Occult bleeding, when present, indicates the need for further investigation. The blood lost in this way is an important contributory factor in iron-deficiency anaemia, but certainly cannot account for all cases. In only one instance in the present series could the diet be regarded as inadequate, and there was no reason to suppose that the diet of anaemic patients, which was similar to that of their non-anaemic colleagues, had a high content of phosphorus or phytic acid. These substances form insoluble complexes with iron salts (Kinney, Hegsted, and Finch, 1949; McCance, Edgecombe, and Widdowson, 1943), and this factor may be important in the iron-deficiency anaemia of the tropics (Foy and Kondi, 1957; Foy, Kondi, and Sarma, 1958), where the diet contains large amounts of phosphorus and phytic acid. It is improbable that the plasma transport mechanism is to blame for primary iron-deficiency anaemia, since the plasma iron-binding capacity has been shown to be more than adequate.

An important point, which has not received attention previously, is that all the patients with primary iron-deficiency anaemia have been between the ages of 18 and 20 and completing a period of adolescent growth, during which the iron requirements are increased. Fig. 2 shows graphically the data of Heath and Patek (1937) and Heilmeyer (1951), which demonstrate how the iron requirements in male subjects increase during adolescence. It is clear that, if primary iron-deficiency anaemia were to develop in male subjects, the most likely time would be between the ages of 18 and 20 years, when they are completing a period during which the iron requirement is increased. After this age, in the absence of blood loss, the intake need only balance the iron excreted from the body. The incidence of anaemia is only 1·1 per cent. among recruits, and these men must have some basic defect which determines that they will become anaemic while the remaining 98·9 per cent. do not. The anaemia could be accounted for by an unusually high excretion of iron. Barer and Fowler (1937) investigated this possibility in patients with hypochromic anaemia, and found that, although the urinary excretion of iron slightly exceeded that found in healthy controls, the increase was too small to produce a state of iron deficiency. The solution to the problem may be found in the observations of

Pirzio-Biroli, Bothwell, and Finch (1958) that healthy and non-anaemic patients, given a meal tagged with radioactive iron, showed a range of uptake of 0·5 mg. to 16 mg. from a standard meal. When these tests were repeated, it was found that in a particular subject the amount absorbed was constant from day to day (Finch, 1958). It seems likely, therefore, that the young men who develop primary iron-deficiency anaemia are those whose iron uptake from food is relatively poor. This point could be settled by the use of modern techniques to compare iron uptake in patients suffering from primary iron-deficiency anaemia with a group of normal control subjects. It is also significant that primary iron-deficiency anaemia is very rare in older men, because this fact supports the

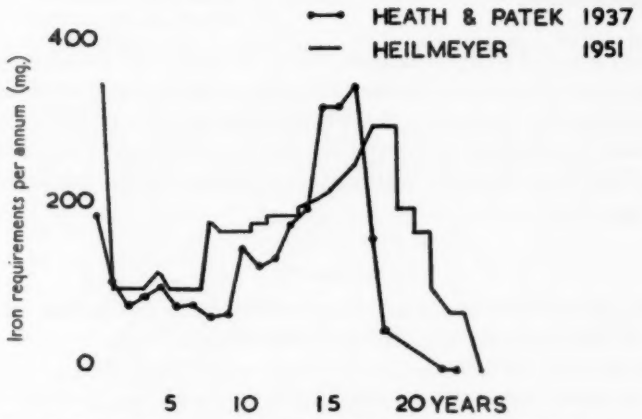

FIG. 2. Iron requirements in male subjects during the first 20 years of life.

idea that increased requirement of iron in adolescence is fundamental to development of the anaemia. It is possible that most of the men who develop iron-deficiency anaemia recover spontaneously when growth ceases and iron requirement is reduced to a level at which the amount of iron absorbed from the diet is sufficient to restore the iron content of the body gradually to normal. The finding that iron salts produced an excellent response, when given orally in doses of about 150 mg. bivalent iron daily, in patients with primary iron-deficiency anaemia (Brumfitt, 1959), may be due to the fact that a sufficient load was given to permit an adequate quantity of iron to be absorbed.

Wintrobe (1956) pointed out that 25 per cent. of his female patients suffering from 'idiopathic' iron-deficiency anaemia had been anaemic since early adult life, and it is possible that this was an anaemia of the same aetiology as in young men, perpetuated by menstrual loss. In order to investigate this point further, haemoglobin estimations were made in a group of recruits to Queen Alexandra's Royal Army Nursing Corps. Unfortunately, because of the smaller intake of women into the forces, only 109 estimations were possible, but the incidence of anaemia was of the same order as in Royal Army Medical Corps recruits, although a much higher proportion of haemoglobin values fell between

11·8 and 14·8 g. per 100 ml. (80 to 100 per cent.). Finally, it is interesting to note that chlorosis, which had many features in common with primary iron-deficiency anaemia, may have had a similar aetiology. This condition was common at the turn of the century, and usually occurred in young women. Habits and environment which led to a poor appetite and diet (Davidson and Leitch, 1934) were probably important, especially in the determination of the severity and duration of the anaemia. Excessive menstrual loss was not an important factor (Ashwell, 1836; Schwarz, 1951). Apart from the greenish complexion, the cases which occurred in men (Ashwell, 1836; Lund, 1875; Hayem, 1900) were presumably identical in aetiology with the cases which have been described.

I am very grateful to my colleague, Dr. F. O'Grady, for valuable discussions during the course of the work. My thanks are due to Colonel R. Spicer for arranging a special ward at the Cambridge Military Hospital to be devoted to the investigation of patients with iron-deficiency anaemia. Dr. E. Knudsen, of the Courtauld Institute, Middlesex Hospital, kindly carried out the estimations of serum iron-binding capacity.

Summary

Iron-deficiency anaemia not associated with organic disease was found in 1·1 per cent. of 2,000 recruits to the Royal Army Medical Corps.

Details are given of the findings in 30 young men suffering from iron-deficiency anaemia in whom exhaustive studies failed to reveal organic disease. When seen three to 12 months after correction of the anaemia with oral iron, no patient had relapsed. Acid had returned to the gastric secretion in many of those who previously had achlorhydria. As a result of these investigations a theory is put forward to explain why *primary* iron-deficiency anaemia occurs.

Primary iron deficiency in young men leads to a state of chronic ill health and loss of efficiency at a critical time in the patient's career. Wider recognition of the condition would lead to early detection and treatment of the illness.

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THE MARFAN SYNDROME[1]

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With Plates 1 to 7

Clinical manifestations of the Marfan syndrome are not uncommon, but are frequently unrecognized. Although disability most often results from ocular and skeletal malformations, premature death is usually from involvement of the cardiovascular system. Early recognition of the syndrome therefore is important. Many papers have been published on individual manifestations, but there has been no British review of the subject. We think that various misconceptions are still held. For example, ectopia lentis and arachnodactyly, though classical features of the syndrome, are sometimes absent and, contrary to earlier opinions, congenital heart disease is not the most common cardiovascular defect. For these reasons we are reporting our experience and reviewing some of the literature.

In 1896 Marfan described in detail a young patient with unusual skeletal deformities and generalized loss of musculature, but no evidence of myopathy. Since birth it had been noticed that she had symmetrical elongation of the extremities, especially the hands and feet. There was a degree of dolichocephaly, with well formed but malplaced ears. No abnormality was noted in the ocular, cardiovascular, alimentary, or respiratory systems. Although unaware of the significance of ocular abnormalities in other members of the family, Marfan noted that one sister had strabismus, and one brother a congenital cataract. He was unable to suggest a cause of the condition, but proposed the descriptive term *dolichosténomélie* (long, thin extremities). Six years later two other French physicians, Méry and Babonneix (1902), described the same patient, and noted further skeletal changes, including a pronounced dorsal kyphoscoliosis. Radiographs were available, and in the opinion of the authors showed some increase of joint space; they suggested that the pathology of the syndrome might be that of hyperchondroplasia. A few months later Achard (1902) presented a case with similar features in a young girl; but instead of contractures she had marked laxity of the ligaments, all the joints being abnormally mobile. No dolichocephaly was present, but the patient showed prominent frontal bossing. Radiography showed that the process of ossification had been completed in a normal manner. A possible familial tendency was indicated, because long hands and feet were reported in one sister, in the mother, and in the maternal grandfather.

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Achard could shed no light on the aetiology of the condition, but he suggested that a more descriptive term for the syndrome would be arachnodactyly (spider fingers). Salle (1912) and Piper and Irvine-Jones (1926) drew attention to the frequency of associated cardiac anomalies. Börger (1914) and subsequent authors have described concomitant ocular abnormalities, particularly ectopia lentis. Since then other authors have recorded related congenital changes in the respiratory and renal systems (see below). Thus the simple musculo-skeletal syndrome first described by Marfan has now become complex, involving many systems and presenting many different clinical forms.

Rados reviewed the observations published up to 1942, adding seven cases of his own and giving 150 references. McKusick (1955*a*, *b*), in excellent reviews, and in his recent book (1956), added the data collected from his study of 50 kinships, in each of which at least one bona fide case of the syndrome had been found. He confirmed the familial pattern, and considered that the several manifestations were probably due to some undefined fundamental defect of connective tissue. Since then cases have been reported singly or in small groups, and altogether about 400 patients have been described, though less than 40 post-mortem examinations appear to have been fully documented. The generally accepted description of the syndrome emphasizes the excessive height, the marked diminution of subcutaneous tissue, and the elongation of the extremities, with arachnodactyly. This, however, is the easily recognized, extreme form of the condition. In many instances the external appearance is not strikingly abnormal, and a suspected case can be confirmed only by certain skeletal measurements and a careful family survey. For example, in the present series only two patients were more than six feet in height. Although many authors have commented on the slender appearance of their patients with the Marfan syndrome, few appear to have noted by how much, if at all, the skeletal measurements vary from those of the normal population.

Skeletal Measurements

Marfan (1896), Méry and Babonneix (1902), and Achard (1902), in comparing various skeletal measurements in their patients with those of normal persons, emphasized the presence of dolichocephaly and elongation of the extremities, especially the fingers and toes. Burch (1936) and Lambie, Shellshear, and Shellshear (1950) performed many body measurements, and confirmed this elongation. Gray (1945), after a careful anthropological study of the physical build of a patient with Marfan's syndrome, commented on the abnormally wide pelvis and narrow shoulders. Hamwi (1951) and McKusick (1955*a*) mentioned two other simple and easily acquired sets of measurements which they considered significant:

1. *The span of the outstretched arms is markedly greater than the height.* McKusick stated, however, that this feature can be found in otherwise normal people. Pearson and Lee (1902), in a study of the inheritance of physical characters in man, measured the height and span in 1,050 male (Fig. 1) and

1,052 female subjects (Fig. 2). It is of interest to note that the span was greater than the height in 622 men (59·2 per cent.), but in only 220 women (20·9 per cent.), being more than three inches greater in 98 men (9·3 per cent.) and in 19

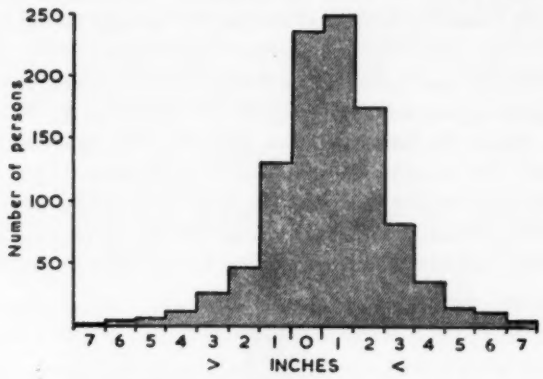


FIG. 1. Relationship of span to height in 1,050 male subjects (Pearson and Lee, 1902).

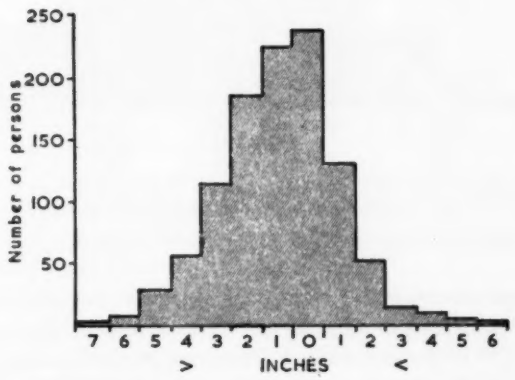


FIG. 2. Relationship of span to height in 1,052 female subjects (Pearson and Lee, 1902).

women (1·8 per cent.). Thus, in the total of 2,102 cases, the span exceeded the height by more than three inches in 117 cases (5·6 per cent.), the extreme being seven inches. Buist (1958) recorded the height and span in 216 healthy male recruits in the armed forces. In 183 (84·7 per cent.) the span exceeded the height, the difference being more than three inches in 27 (12·5 per cent.), and the extreme being six and a half inches. Thus this measurement, by itself, is of no value in determining the presence of the Marfan syndrome, but it may be helpful when carrying out family surveys. The span may or may not exceed

the height in normal persons, but in our experience the span has not been less than the height in any proven case of the syndrome.

2. *The lower segment (pubis to heels) is longer than the upper segment (pubis to vertex).* Lawrence (1958) recorded the sitting and standing height in a group of 378 normal men between the ages of 40 and 50. In only 20 cases (5·3 per cent.) was the lower segment greater than the upper segment by more than two inches, the extreme case being three inches. Buist (1958), in comparing the lower and upper segments in his group of 216 men (Fig. 3), found 19 cases (8·8 per cent.) in which the lower segment exceeded the upper segment by more than two inches, the extreme being five and a half inches. In only two of these cases, however, did he also find that the span was greater than the height by more than three inches. Neither case was considered to have features of the Marfan syndrome, although this possibility was specifically considered.

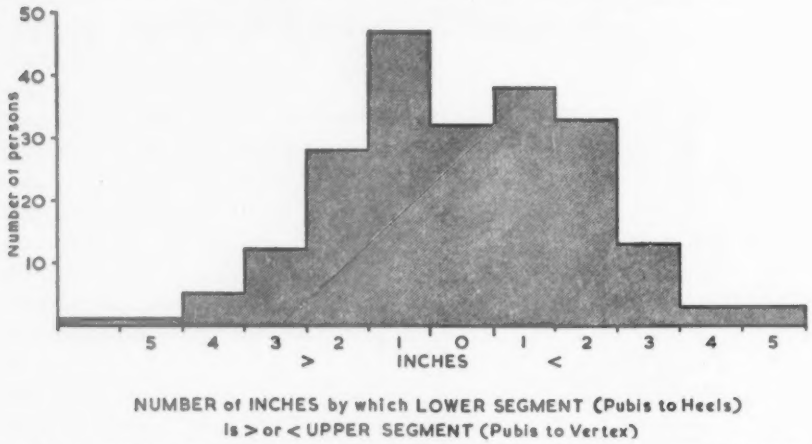


FIG. 3. Relationship of lower to upper segment in 216 male subjects (Buist, 1958).

Arachnodactyly. In reviewing published reports it is difficult to determine what criteria have been considered by the various authors when using the term arachnodactyly. With common usage the term now erroneously includes other skeletal changes, particularly the elongation of the extremities. Arachnodactyly means 'spider fingers', but the diagnosis has most often been based solely on impression, which can be misleading. Many families are noted for the inheritance of long hands and feet in the absence of other skeletal abnormalities. Conditions which produce loss of muscle and subcutaneous tissue of the hands will produce deceptively long and thin fingers, which might be described as 'spidery' in appearance.

Metacarpal index. In an attempt to be more objective in diagnosing arachnodactyly, a study was made of the radiographic appearances of the hands in 20 cases of Marfan's syndrome and in 100 unselected normal people. In each right hand the length of the second, third, fourth, and fifth metacarpals was measured in millimetres. At the exact mid-point of each shaft the breadth was also

measured in millimetres, and this was divided into its length. The resulting figures, from each of the four metacarpals, were added together and divided by four to give an average, the metacarpal index (Table I). In the normal group the index varied from 5·4 to 7·9, with 80 per cent. in the range 7·0 to 7·9. In the Marfan group the range varied from 8·4 to 10·4, with 70 per cent. in the range 8·4 to 9·4. There appears to be a significant difference in the two groups, and the metacarpal index may prove an additional aid in diagnosing doubtful cases of arachnodactyly, and also in family surveys.

TABLE I

Marfan syndrome: 20 cases

Metacarpal index	8·4–8·9	9·0–9·4	9·5–9·9	10–10·4
Number of cases	7	7	4	2

Normal subjects: 100 cases

Metacarpal index	5·4–5·9	6·0–6·4	6·5–6·9	7·0–7·4	7·5–7·9
Number of cases	1	3	16	39	41

In two young patients measurements were available over a period of three years, and are presented in Table II.

TABLE II

	Year	*Height (inches)*	*Span (inches)*	*Lower segment (inches)*	*Meta-carpal index*
G.R. A boy	1955	67¾	72	35	9·8
aged 14 years	1956	70	75	37	10·1
	1957	72½	77	38	10·3
M.C. A girl	1955	60	63	32½	9·0
aged 9 years	1956	65	67½	35	9·3
	1957	68	71	36½	9·6

It is interesting to note that the relationships of height to span and of upper to lower segment have remained approximately the same, whereas the metacarpal index has steadily increased.

Conclusions. It is suggested, therefore, that the term arachnodactyly should be reserved for patients with long, thin fingers and, as recommended above, with a metacarpal index greater than 8·4. Should such a patient also have a span exceeding the height by more than three inches, together with a lower segment greater than the upper segment by more than two inches, the diagnosis of the Marfan syndrome should be considered. A complete physical examination, and if necessary a family survey, should then be carried out to confirm the diagnosis.

Musculo-skeletal Manifestations

The available members of 18 families, in each of which at least one member had unequivocal evidence of the Marfan syndrome, were studied. A remarkable number of skeletal abnormalities were noted in 40 members (Table III). It is thought that the features in column A are probably related to the syndrome,

as they appear to be the result of tissue and ligament laxity, whereas those in column B may be only incidental. In five cases the general appearance of extreme loss of subcutaneous tissue and elongation of the extremities was sufficient to suggest the diagnosis. The remaining 35 subjects were not remarkable in external appearance. In the group of 40 there were 24 male and 16 female patients, their ages ranging from nine to 54 years. Eighteen had ocular

TABLE III

Skeletal Abnormalities

	A	*B*
Skull:	Dolichocephaly Deformed sella turcica High palate	Frontal bossing Prognathism Malplaced ears Irregular dentition
Spine:		
Cervical	Loss of normal curve	Spina bifida Vertebral body fusion
Dorsal	Kyphosis Scoliosis Rotation Slipping of vertebrae Compression fractures Osteochondral dystrophy	Epiphysitis
Lumbar	Spondylolisthesis Alteration in shape of vertebral bodies	Spina bifida
Pelvis:	Pelvic distortion Sacro-iliac sclerosis	Hip dysplasia Congenital fusion of sacro-iliac joints
Chest:	'Pigeon' deformity 'Funnel' deformity Unilateral deformity	Hole in sternum (failure of fusion)
Upper limbs:	Arachnodactyly Extreme laxity of joints	Syndactyly Unequal size of scapulae
Lower limbs:	Slipped epiphysis High patella Ankle deformity Long unstable feet Talipes equinovarus	Deformity of distal phalanges

changes; 14 had cardiovascular defects, and 20 had complained of musculoskeletal pain. As very little information is available regarding the 'rheumatic' element of the syndrome, it is justifiable to discuss these 20 in more detail. Table IV shows the presenting symptoms, the initial diagnosis, and the skeletal abnormalities, other than arachnodactyly, in each case.

Symptoms. The most common symptom was back pain, present in seven patients. Four had received treatment for 'fibrositis', and two were considered to have ankylosing spondylitis, including one who received deep X-ray therapy without clinical benefit. The seventh case was undiagnosed. Joint pain and effusions were noted in five patients. In three the joint condition was tentatively considered to be tuberculous in origin. One received chemotherapy, which was abandoned when a knee biopsy showed no histological evidence of tuberculosis.

One of the remaining two cases was diagnosed as rheumatic fever, and the other as rheumatoid arthritis, which was later disproved. Hip-joint pain was prominent in two patients, and both had congenital dysplasia of the hips. In one the original diagnosis of Still's disease was altered later to ankylosing spondylitis, although in fact the patient showed no real evidence of either disease. Metatarsalgia was the only complaint in three patients, and they had typical long, unstable feet. Rheumatoid arthritis was suggested in one patient with cervical stiffness and pain; another patient with vague undifferentiated pain was considered to be psychoneurotic. In only one case was the correct diagnosis of Marfan's syndrome made before the survey.

TABLE IV

Musculo-skeletal Manifestations in the Marfan Syndrome

No.	*Age (years)*	*Symptoms*	*Initial diagnosis*	*Skeletal abnormalities*
Male patients:				
1	21	Joint effusion	Tuberculous joint	Lax ligaments. High patellae
2	48	Stiff neck	?Rheumatoid arthritis	Dorsal kyphosis
3	18	Joint pains	Rheumatic carditis	'Pigeon' chest. Kyphosis. Spina bifida
4	40	Joint effusions	Rheumatoid arthritis	'Funnel' chest. Kyphosis. Defective lumbar vertebrae
5	46	Low back pain	Undiagnosed	Dorsal kyphosis
6	16	Joint effusions	Tuberculous joint	Mild scoliosis
7	54	Low back pain	Fibrositis	Scoliosis. Posterior slipping of L2 on L3
8	41	Finger stiffness	Acrocyanosis	Scoliosis. Sacro-iliac sclerosis
9	24	Low back pain	Ankylosing spondylitis	Congenital fusion of sacro-iliac joints
10	27	Low back pain	Ankylosing spondylitis	Sclerosis of sacro-iliac joints
11	15	Joint effusion	Tuberculous joint	'Funnel' chest
12	45	Low back pain	Fibrositis	Scoliosis
Female patients:				
No.				
1	54	Low back pain	Fibrositis	Lumbar scoliosis
2	27	Hip-joint pain	Still's disease. Ankylosing spondylitis	Osteoarthritis of hips. Flattening of dorsal vertebrae
3	9	Locomotor disability	Marfan syndrome	'Pigeon' chest. Talipes equinovarus
4	10	Metatarsalgia	'Growing pains'	Lumbar scoliosis
5	22	Metatarsalgia	Foot strain	Dorsal scoliosis
6	48	Low back pain	Fibrositis	Kyphosis; scoliosis; fused vertebrae
7	22	Hip-joint pain	Congenital dislocation of hips	'Funnel' chest. Deformed femoral heads
8	33	Vague joint pains	Psychoneurosis	Dorsal scoliosis

Skeletal changes consist of the abnormalities that one would expect to find in patients with lax, unstable joints, subjected to stress and strain. Once the inherited fault in the collagen tissue is established, the subsequent deformities are probably entirely mechanical, and are often aggravated by unsuitable occupations. This is exemplified in the cases shown in Table V, which together represent most of the skeletal deformities described in the Marfan syndrome. The following additional skeletal deformities were present in five of the cases described in greater detail in the cardiac section:

(Tables V and VI, Case 10. H. C.) Unusual defect in the sternum.

(Table VI, Case 14. T. T.) Enlarged sella turcica.

(Table VI, Case 15. M. W.) Grossly depressed chest (Plate 3, Fig. 15); some flattening of the sella turcica.

(Table VI, Case 17. L. C.) Pseudo club feet (Plate 3, Fig. 16).

(Table VI, Case 20. A. N.) Spina bifida of the cervical spine; kyphosis and chest deformity.

TABLE V

Clinical Features in the Musculo-skeletal Series

Case number	Sex	Age (years)	Features: Symptoms	Features: Skeletal	Features: Cardiovascular	Features: Ocular	Excess (inches) of: Span over height	Excess (inches) of: Lower over upper segment	Metacarpal index	Family members affected
1 D. G.	M	40	Back pain and sciatica	Congenital foot and ankle deformities. Gross deformity of the lumbar spine with sacro-iliac joint sclerosis (Plate 1, Fig. 6)	Bradycardia	Ectopia lentis. Bilateral cataracts. Severe degree of myopia	3½	2½	10·2	Daughter
2 L. G.	F	16	None (Family survey)	Congenital foot deformities. Kyphosis. Compression fracture 7th dorsal vertebra	..	..	3	5½	10·4	Father (Case 1)
3 D. R.	M	54	Back pain and sciatica. Angina of effort	'Pigeon-chest' deformity. Posterior slipping of 2nd lumbar vertebra (Plate 1, Fig. 7). Genu valgum	Dilatation of ascending aorta	Ectopia lentis	4	4½	8·9	Son
4 G. R.	M	16	None (Family survey)	High-arched palate. Scoliosis in dorso-lumbar region. Unilateral chest deformity. Arachnodactyly (Plate 1, Figs. 8, 9)	..	Ectopia lentis	4½	2½	9·8	Father (Case 3)
5 M. C.	F	9	Metatarsalgia	Dolichocephaly (Plate 2, Fig. 10). High-arched palate. Dorsal kyphosis. 'Pigeon-chest' deformity	..	Ectopia lentis	3	5	9·0	Orphan
6 J. L.	M	21	Intermittent hydrarthrosis	Dorsal scoliosis. High patellae (Plate 2, Fig. 11). Excessive laxity of all joint ligaments	..	Ectopia lentis	4½	2½	9·4	None available
7 J. B.	M	16	Pain and swelling of both knees	Severe depression deformity of the chest. Upward dislocation of patellae. Osteochondritis of dorsal and lumbar vertebrae. Deformities of the distal phalanges (Plate 2, Fig. 12). Sclerotic changes in the sacro-iliac joints	..	Myopia and iridodonesis	4	5½	9·4	Sister
8 C. B.	F	48	Back pain	Congenital fusion of 2nd and 3rd cervical vertebrae (Plate 3, Fig. 13). Dorso-lumbar scoliosis. 'Pigeon-chest' deformity	..	Myopia	5	4	9·4	Daughter
9 M. B.	F	22	Intermittent hip pain	Depressed sternum. Dorso-lumbar scoliosis. Gross deformity of the femoral heads (Plate 3, Fig. 14)	..	Myopia and iridodonesis	6	3½	9·7	Mother (Case 8)
10 H. C.	M	55	Dyspnoea on exertion. Headaches	Prognathism. 'Funnel' depression of chest. Congenital hole in sternum. Dorsal kyphosis	Hypertension. Aneurysm of arch of aorta	Myopia	6	5	8·4	2 sons and 1 daughter

It will be seen that the Marfan syndrome manifests itself in many ways. The main presenting sign or symptom will generally determine to which department the patient is referred. Patients with ocular, cardiac, and musculo-skeletal defects will be referred to ophthalmic, cardiac, and orthopaedic or rheumatic diseases clinics respectively. It is obviously important to recognize all cases early, so that any deformities present can be corrected or adequate measures taken to prevent increasing deformity. For example, without a significant family history, the patient L. G. (Case 2) would not have been examined for

manifestations of the syndrome, and her symptomless fracture might have progressed until painful symptoms appeared, by which time the corrective procedure would have been less effective.

Abnormal findings in the blood appear to have been recorded in few previous publications. Achard's (1902) patient suffered from the 'anaemia of chlorosis'. Acute bacterial endocarditis with anaemia was reported in one case by Olcott (1940) and in two cases by Tung and Liebow (1952). Occasional elevation of the erythrocyte sedimentation rate was noted in one case by Wilson (1957). Anaemia and an elevated erythrocyte sedimentation rate were recorded by Booth, Loughridge, and Turner (1957) in two patients, each of whom had congenital renal lesions and died from uraemia. In the present series 10 patients showed significant elevation of the erythrocyte sedimentation rate; two had moderate anaemia, and one had a high fibrinogen level. Incidental infections might have accounted for these changes in two cases, and Henoch's purpura in a third, but no adequate explanation was found in the remainder.

Cardiovascular Manifestations

Most of the cases in this series (Table VI) were found during the routine examination of patients attending the Cardiac Department of the Western General Hospital, Edinburgh, during a period of three years. They include examples of dilatation of the aorta, dissecting aneurysm, aortic incompetence, dilatation of the pulmonary artery, atrial septal defect, mitral stenosis, heart block, paroxysmal tachycardia, and dextroversion. Rados (1942) in his review found records of cardiovascular involvement in 63 out of 204 cases, and concluded that such involvement was second in frequency only to the ocular manifestations. It is evident, however, from the descriptions recorded that in most cases no detailed assessment had been made in regard to the heart, the diagnosis often being that of 'vitium cordis'. The information given is inadequate for precise diagnosis, or indeed for the drawing of any conclusions. The frequency with which the cardiovascular system is involved in patients with the Marfan syndrome has been variably reported as 30 to 60 per cent., but for a number of reasons it is impossible to establish the true incidence. Many patients are seen by ophthalmologists, orthopaedic surgeons, or others, without undergoing a cardiac examination. Some cases with minor manifestations of the syndrome, may be missed entirely. In many cases a praecordial murmur can probably be attributed to a skeletal deformity of the chest or spine; in such cases, again, extracardiac sounds are often present and may be misinterpreted. Autopsies have been relatively rare, and in such series the recorded incidence of cardiovascular anomalies has been high; this could, however, be largely due to the fact that such anomalies, when they occur in patients with the Marfan syndrome, are most likely to be the cause of death. It used to be thought that congenital heart disease, especially an atrial septal defect, was the most common cardiovascular anomaly, but now it seems to be generally agreed that dilatation of the aorta occurs more frequently (Table VII). At post-mortem

TABLE VI

Clinical Features in the Cardiovascular Series

Case number	*Sex*	*Age (years)*	*Symptoms*	*Features*			*Excess (inches) of*		*Meta-carpal index*	*Family members affected*
				Cardiovascular	*Skeletal*	*Ocular*	*Span over height*	*Lower over upper segment*		
3 D. R.	M	54	Back pain and sciatica. Angina of effort	Dilatation of ascending aorta (Plate 4, Fig. 17)	Arachnodactyly. 'Pigeon-chest' deformity. Posterior slipping of 2nd lumbar vertebra (Plate 1, Fig. 7). Genu valgum	Ectopia lentis	4	4·5	8·9	Son
10 H. C.	M	55	Headaches	Hypertension. Dilatation of arch of aorta	Arachnodactyly. Prognathism. 'Funnel' depression of chest. Congenital hole in sternum. Dorsal kyphosis	Myopia	6	5	8·4	2 sons and 1 daughter
11 C. L.	M	49	Hemiplegia	Dilatation of descending arch of aorta (Plate 4, Fig. 18)	Pes cavus. Kyphosis. Leg ulcers	Congenital ptosis. Corneal opacities	4	7	..	Mother
12 J. G.	M	41	Acute cardiac failure	Aortic incompetence. Aneurysm of descending aorta. Progressive cardiac enlargement. ?Myocarditis	Arachnodactyly. 'Pigeon-chest' deformity. Talipes equinovarus	Ectopia lentis	..	..	..	..
13 A. C.	M	17	Cardiac pain	Rupture of aorta (Plate 5, Fig. 20). Haemopericardium. Fenestrated valve cusps. Myxomatous nodules on valve cusps (Plate 5, Fig. 19)	Arachnodactyly. Dolichocephaly. High-arched palate. Abnormally mobile joints. Kyphosis. 'Funnel' deformity of chest	Ectopia lentis	..	..	..	..
14 T. T.	M	46	None (Routine X-rays)	Dilatation of pulmonary artery (Plate 6, Fig. 21). Aneurysm of abdominal aorta	Arachnodactyly. Large sella turcica. High-arched palate. High patellae. Dorsal kyphosis	Bilateral choroiditis in region of macula	5	2	8·6	Son
15 M. W.	F	24	Palpitation	Paroxysmal tachycardia (Fig. 4, p. 37)	Arachnodactyly. Shallow sella turcica. 'Funnel' deformity of sternum (Plate 3, Fig. 15). Scoliosis	Ectopia lentis	..	..	..	..

16 E. M.	M	38	Acrocyanosis	Heart block (Fig. 5, p. 37). Myocardial ischaemia	Arachnodactyly. High-arched palate. Scoliosis. Sacro-iliac joint sclerosis. Ulcers in legs	Astigmatism. Myopia	4·5	3	9·4	?Father
17 L. C.	F	10	Dyspnoea on exertion	Atrial septal defect	Arachnodactyly. High-arched palate. 'Pigeon-chest' deformity. Pseudo club foot (Plate 3, Fig. 16). Irregular vertebral bodies	..	3·5	5·0	..	Father
18 D. M.	M	21	None (Routine examination)	Atrial septal defect	High-arched palate. 'Pigeon-chest' deformity. Pes planus	..	3·5	1·5	..	Father
19 G. W.	F	24	Dyspnoea on exertion	Mitral stenosis. Aortic incompetence	Arachnodactyly. High-arched palate. Dorsal kyphosis. 'Funnel' deformity of chest	Ectopia lentis. Retinal detachment	..	..	8·9	Mother, brother, and sister
20 A. N.	M	19	Dyspnoea on exertion	Mitral stenosis	Arachnodactyly. High-arched palate. 'Pigeon-chest' deformity. Dorsal kyphosis. Spina bifida	Myopia. Strabismus. Astigmatism	4	8	9·0	Father
21 R. O.	M	21	None	Dextroversion (Plate 6, Fig. 22)	'Pigeon-chest' deformity. Wedged lumbar vertebra. Underdeveloped left hand and shoulder girdle	..	..	3	..	..
22	M	22	Subarachnoid haemorrhage	Hypertension (polycystic kidney)	High-arched palate. Prognathism	..	2	2·5	..	?Brother

examination endocardial lesions are often found, and probably account for most of the murmurs noted during life. The conditions listed in Table VIIB may be associated with the Marfan syndrome more frequently than they occur in the general population. It seems improbable, however, that they are due to the fundamental defect in ground-substance which is believed to be responsible for the changes in the aorta or pulmonary artery. It is more probable that they occur as associated, but not directly related, congenital defects, and for this reason they have been listed separately.

TABLE VII

Cardiovascular Manifestations of the Marfan Syndrome

A. Relationship likely to be direct:	
Aorta	Localized dilatation of ascending aorta Dilatation of the arch or descending aorta Dilatation of the sinuses of Valsalva Abnormalities of the aortic valve cusps Dilatation of the aortic valve ring with incompetence Rupture of the aorta, with or without dissecting aneurysm
Pulmonary artery	Dilatation Rupture
Valvular lesions	Dilatation of valve ring Fenestration of cusps Endocardial changes
Myocardial lesions	
Conduction defects	Heart block Bundle branch block
Arrhythmias	Auricular fibrillation Paroxysmal tachycardia
B. Cardiovascular defects which may be associated with the Marfan syndrome but without a direct relationship:	Coarctation of the aorta Septal defects: Atrial Ventricular Patent ductus arteriosus Dextroversion Rheumatic mitral disease

Aorta

The first definitive description of the two important aortic complications of the Marfan syndrome, namely diffuse dilatation (Baer, Taussig, and Oppenheimer) and dissecting aneurysm (Etter and Glover) appeared in 1943. In 1947 Uyeyama, Kondo, and Kamins reported the post-mortem findings in a man who died from rupture of a dissecting aneurysm, and summarized nine previously recorded cases of arachnodactyly with cardiovascular defects, giving 66 references. In 1951 Marvel and Genovese reported a case of the Marfan syndrome with fusiform dilation of the aorta, and summarized 28 previous cases of the syndrome in which post-mortem examinations had been made. In 25 of these cases cardiovascular defects were found, and in 15 there was an aneurysm of the aorta. McKusick (1955*b*) reviewed the various abnormalities which may be found in the Marfan syndrome; recently, since the condition has become more

generally recognized, numerous cases have been reported. In most instances the histological features of so-called medio-necrosis (discussed below) have been found. There are earlier reports of fusiform dilatation, with or without dissection, occurring in young people, in which no reference to ectopia lentis or arachnodactyly is made; but various skeletal deformities, and also the histological changes characteristic of medio-necrosis, were present, and it seems highly probable that the cases described were examples of the Marfan syndrome (Bronson and Sutherland, 1918; Davies, 1941; Yettra and Lasky, 1947; Horder, 1908; Holland and Bayley, 1940).

Table VII gives the characteristic abnormalities of the aorta which may occur. Most of these conditions are due to medial degeneration in the wall of the aorta, and in life may be brought to light in one of the following ways:

1. *Radiographic examination of the chest.* Dilatation of the aorta may be detected on routine radiographic examination for some other condition, or after recognition of some manifestation of the Marfan syndrome.

2. *Auscultation of the heart.* An early diastolic murmur from aortic incompetence may be due to dilatation of the valve ring or distortion of the cusps. Sometimes an aortic systolic murmur results from roughening of the cusps.

3. *Cardiac failure.* Cardiac failure may be the manner in which the condition first comes to notice, and may be secondary to aortic incompetence, with or without a myocardial factor, as discussed below.

4. *Rupture of the aorta* into the pericardium or pleura may be responsible for sudden death. A dissecting aneurysm may occur with or without subsequent rupture.

Dilatation of the aorta

Ascending aorta. It is noteworthy that dilatation occurs most frequently at the base of the aorta, next in the ascending arch, and progressively less frequently towards the peripheral parts, probably because the proximal part of the aorta is subjected to the greatest pressure. Since this portion is within the pericardial sac, dilatation may not at first be obvious radiographically. Valvular incompetence from dilatation of the ring may be considerable at this stage. Undue pulsation just above the right atrium may, however, be seen on radioscopy, despite the absence of obvious dilatation, which is likely to increase with time.

A man aged 54 (Case 3, Table VI), with angina of effort and increasing shortness of breath, was found on radiography to have dilatation of the ascending aorta (Plate 4, Fig. 17*a*, *b*). There was no evidence of aortic incompetence.

Aortic arch. The following two cases from our series illustrate the remarkable degree of aortic dilatation which may be found in a symptomless patient.

A man aged 55 (Case 10, Table VI) was referred for an opinion because of severe frontal headaches. He was known to be hypertensive (blood-pressure 210/140). Radiography showed irregular fusiform dilatation of the aorta from the level of the arch almost to the diaphragm. The Wassermann reaction was negative in blood and cerebrospinal fluid.

A man aged 49 (Case 11, Table VI) sustained a left hemiplegia in 1954, when he was found to be hypertensive (blood-pressure 240/140). He had suffered from repeated ulceration of the feet and legs since the age of 14. Radiography showed fusiform dilatation of the ascending and descending arch of the aorta (Plate 4, Fig. 18). The Wassermann reaction was negative in blood and cerebrospinal fluid.

Descending aorta. A man aged 46 (Case 14; see page 34) had aneurysmal dilatation of the abdominal aorta as well as dilatation of the pulmonary artery.

Diagnosis. From the clinical point of view localized dilatation of the ascending aorta is most likely to be due to syphilis or medial degeneration, but may also occur in association with aortic stenosis or coarctation of the aorta. When dilatation of the arch of the aorta is observed radiographically, the diagnosis is usually considered to lie between atherosclerosis and syphilitic aortitis. If there is no saccular aneurysm, and the Wassermann reaction is negative, a presumptive diagnosis of atherosclerosis is usually made. If dilatation of the aorta is the only finding, suggesting the presence of atheroma, or if the condition is observed in childhood, adolescence, or middle life, the possibility of the Marfan syndrome should be remembered, and other evidence sought in the patient or in members of the family.

Aneurysmal dilatation of the sinuses of Valsalva

The sinuses of Valsalva are intracardiac structures and hence not visible on an ordinary radiograph, though plainly delineated by angiocardiography. Dilatation of the sinuses in association with the Marfan syndrome was found at autopsy in cases reported by Weill (1932), Moses (1951), and McKusick (1955*b*). The pathological process concerned seems to be an extension of the medial necrosis present in the aorta. In 1955 Steinberg and Geller reported three cases diagnosed in life by angiocardiography. In view of the fact that these aneurysms were discovered as a result, apparently, of routine angiography in patients with the Marfan syndrome, it is probable that many more cases would be disclosed if this method of examination were carried out more frequently.

Aortic valve cusps

The changes which may be present are saccular dilatation, fenestration, thickening and nodulation, or bacterial endocarditis. The aortic cusps may share in the connective tissue defect which is present in the media of the aorta and, as a result of stretching, considerable sacculation may result. This is well shown in one of the cases illustrated by McKusick (1955*b*). Fenestration may likewise result, and was present in one of our cases (Plate 5, Fig. 19). Thickening and nodulation of the margins of the cusps may occur (Plate 5, Fig. 19), as in the mitral valve, from mucoid degenerative changes, which can be distinguished from those which result from rheumatic fever, and are referred to below. Bacterial endocarditis superimposed upon these valvular changes has

been reported several times (Vivas-Salas and Sanson, 1948; Olcott, 1940; McKusick, 1955*b*).

Aortic incompetence

The causes of aortic incompetence include rheumatic fever, bacterial endocarditis, syphilis, atherosclerosis, trauma, dissecting aneurysm, and medio-necrosis as in the Marfan syndrome. An early diastolic murmur from aortic incompetence is a well recognized finding in cases of dissecting aneurysm of the aorta from any cause, and as such may occur as a manifestation of the Marfan syndrome. Apart from dissecting aneurysm, aortic incompetence in this syndrome may result from dilatation of the valve ring, from sacculation and fenestration of the body of the cusps, or from thickening and nodule formation in the cusp margins. As mentioned above, the valve ring and adjacent intrapericardial part of the aorta are first affected, and severe aortic incompetence may be present before much dilatation of the aorta is demonstrable. Evidence of the Marfan syndrome should be sought in any patient in whom aortic incompetence is found without obvious cause. It is important that all such patients should be kept under observation, because the degree of aortic incompetence is often progressive, and what was taken to be an unimportant valvular defect may steadily or rapidly increase until cardiac failure ensues.

A man aged 41 (Case 12, Table VI) was admitted to hospital in cardiac failure. Two years previously he had been in the same hospital on account of haematemesis, and at that time a large pulsating aneurysm of the descending aorta was found; there was no cardiac enlargement, and the only abnormality found in the heart was a systolic murmur. When next admitted, in addition to cardiac failure, he had considerable cardiac enlargement. The systolic murmur was louder, most pronounced at the apex, and accompanied by a thrill. An aortic diastolic murmur had developed. The degree of aortic incompetence was not considered to be severe, because the pulse was not collapsing in type, the blood-pressure was only 130/70, and the electrocardiogram showed no evidence of left ventricular hypertrophy. Skeletal manifestations of the Marfan syndrome were recognized, and he had ectopia lentis. Shortly after admission he died from rupture of the aneurysm. There was no autopsy. It seems doubtful whether the degree of aortic incompetence present could account for the rapid downhill course, and reference is made to this case in the discussion on myocarditis.

Rupture of the aorta

Rupture of the aorta, with or without a dissecting aneurysm, is now a well recognized complication of the Marfan syndrome, and the histological changes in such cases are similar to those found in dissecting aneurysm occurring apart from this syndrome. The clinical features will not be described here, but from the growing number of published cases it is clear that evidence of the Marfan syndrome should be sought in all instances.

A male student aged 17 (Case 13, Table VI) was admitted to hospital, six days before his death, because of the sudden onset of severe retrosternal pain

and breathlessness. On admission there was distension of the neck veins, apparent enlargement of the heart, and a loud apical systolic murmur. Many skeletal abnormalities were present, and also ectopia lentis. A clinical diagnosis of the Marfan syndrome with rupture of the aorta was made, and he died suddenly on the fifth day after admission. At autopsy about 1,000 ml. of blood-clot distended the pericardial sac. There was slight fenestration of the cusps of the pulmonary, tricuspid, and aortic valves, and several pinkish-grey, semi-translucent nodules were present on the atrial surface of the valves. The aortic cusps showed thickened, rolled, free margins, with smooth nodular swellings (Plate 5, Fig. 19). The aortic valve ring and the ascending aorta were markedly dilated, and, to a lesser extent, the aortic arch. 2·5 cm. above the aortic ring was a transverse tear, 1·5 cm. long, through the aortic wall (Plate 5, Fig. 20), and from this region to the arch partially organized ante-mortem thrombus was adherent to the outer wall of the aorta, but there was only slight evidence of dissection of the walls. Basophilic metachromatic material, resembling normal ground-substance but considerably increased in amount, was present in the wall of the aorta, especially in the media and in the ascending aorta. In relation to these deposits there was considerable diminution in the number of elastic fibres, and also to some extent of reticulin and muscle-fibres (Plate 7, Fig. 23). The small nodules in the valve cusps had a fibrous, myxomatous structure, and showed no evidence of rheumatic or other inflammation.

Pulmonary artery

Dilatation of the pulmonary artery may occur in association with pulmonary stenosis, pulmonary hypertension from any cause, increased pulmonary blood-flow from a left-to-right shunt, or 'idiopathically' as an isolated finding without evidence of heart disease. It is in this last group that the possibility of the Marfan syndrome should be considered. Dilatation, with or without rupture, may result from medial degeneration similar to that responsible for some cases of dilatation of the aorta. Deterling and Clagett in 1947, in a detailed review of the causes of dilatation of the pulmonary artery, made no mention of this possibility. The first case to be recognized was that of Lillian (1949), in a girl of 17 years with congenital cystic disease of the lungs and patency of the ductus arteriosus. Other cases have been reported by Wilkinson (1940) and Anderson and Pratt-Thomas (1953). A more recent case is referred to below in the section on patent ductus arteriosus (Bingle, 1957).

A man aged 46 (Case 14, Table VI) was found to have dilatation of the pulmonary artery on routine radiography (Plate 6, Fig. 21). Three years later he developed signs of a large pulsating aneurysm of the abdominal aorta, and stigmata of the Marfan syndrome were recognized. Leakage of the abdominal aneurysm into the duodenum occurred, and the patient died after surgical treatment.

Pathological Changes in the Aorta and Pulmonary Artery

The only adequate pathological studies in the Marfan syndrome have been in relation to the aorta and pulmonary artery, and in both vessels the changes are similar. The principal changes found are those first described by Erdheim

(1930) as medio-necrosis aortae idiopathica cystica, and consist of gross distortion of the normal architecture of the media, with fragmentation of elastic fibres, degeneration of muscle-fibres, replacement fibrosis, and the appearance of spaces filled with mucoid material. The staining reactions of this metachromatic material suggest that it is similar to or identical with normal ground-substance, but considerably increased in amount (Plate 7, Fig. 23 (from Case 13, Table VI)). There is no inflammatory reaction. The precise description of the changes found in the Marfan syndrome varies. Some authors have emphasized the formation of greatly dilated vascular channels penetrating the media from the adventitia. Macleod and Williams (1956) objected to the term cystic medio-necrosis because there is no true cyst formation and little necrosis, the essential morphological change being the abnormal accumulation of mucoid material replacing muscle, collagen, and elastic fibres. Some have considered that vascular changes are primary, and others that the first and fundamental change consists of degeneration of elastic lamellae. A developmental defect in the media was considered to be the cause by Baer, Taussig, and Oppenheimer (1943) and Tobin, Bay, and Humphreys (1947), and a defect in the nutrient vessels by Uyeyama, Kondo, and Kamins (1947) and Schnitker and Bayer (1944). McKusick (1955*b*) favoured an abiotrophy; Sloper and Storey (1953) felt that the primary defect was in the ground-substance, and of endocrine origin. Similar pathological changes have been produced experimentally by intravenous injections of histamine and of adrenaline, by destruction of the vasa vasorum with heat, acids, or clamps, and, more recently, simply by feeding with a chemical compound (Bean and Ponseti, 1955). The last-mentioned work is extremely interesting. After the production of experimental lathyrism in growing rats, Ponseti noted that a diet rich in sweet pea meal resulted in multiple skeletal deformities, and the animals often died of spontaneous dissecting aneurysm associated with degeneration of the media. Subsequent work has shown that the substance responsible is β-aminopropionitrile. The common fault in the tissues is a defect in ground-substance. Bean and Ponseti noted similar changes in the skeleton and aortic wall in the Marfan syndrome, and suggested that they might be due to some inborn error of metabolism or dietetic factor.

Myocarditis

In 1951 Whitfield, Arnott, and Stafford reported the case of a man of 35 with Marfan's syndrome, who had been well until six months before his death. He then began to notice tiredness, and later undue breathlessness on exertion. He was admitted to hospital in cardiac failure, made no response to treatment, and developed terminal auricular fibrillation. The clinical diagnosis was severe idiopathic myocarditis. At autopsy the heart weighed 910 g. All the chambers were dilated. The valves and coronary arteries were normal. The left ventricle wall was 15 mm. and the right ventricle 4 mm. thick. The aorta was somewhat smaller than usual for a man of this age (15 mm. wide instead of the predicted

16·7 mm.). The myocardium showed fine, diffuse fibrosis, most marked in the interventricular septum, with scattered areas of destruction of muscle-fibres and replacement by collagen and fibrous tissue. This was a clear instance of myocardial failure in a patient with the Marfan syndrome, and the authors considered that it was the first such case to be described. In other reported cases of the Marfan syndrome there is occasional mention of microscopic changes in the myocardium, but this finding, apparently, has in no case been considered significant. Tung and Liebow in 1952 described a girl of five years, with skeletal changes of the Marfan type, who died in congestive cardiac failure. Post-mortem examination showed myxomatous thickening of the endocardium of the mitral and aortic valves, with medio-necrosis of the aorta and aneurysmal dilatation of the sinuses of Valsalva. From the description given the degree of aortic incompetence would not seem sufficient to account for the severity of her cardiac failure, and, although no comment is made as to its possible significance, there is reference in the histological report to granulomatous foci in the myocardium with central fibrinoid necrosis. In the description by Fischl and Ruthberg (1951) of a 24-year-old woman, with ectopia lentis, a high-arched palate, and long thin extremities, who died of cardiac failure, post-mortem examination showed a heart weighing 750 g., with a saccular aneurysm at the base of the aorta and coarctation. Histological examination showed cystic medio-necrosis, and mention was made of moderate fatty degeneration and diffuse fibrosis of the myocardium. It is probable that insufficient attention has been paid to the myocardium in some cases of the Marfan syndrome because the degree of cardiac enlargement, the severity of cardiac failure, and its rate of progression, have seemed out of proportion to the anatomical defects. This is illustrated in one of the cases from our series which, unfortunately, is incomplete because permission for post-mortem examination was not obtained. The patient is referred to in the section on aortic incompetence (Case 12). Progressive cardiac enlargement and congestive failure seemed quite out of proportion to the degree of valvular regurgitation, and hence a myocardial factor was inferred.

Arrhythmias

McKusick (1955*b*) stated that in his series of cases auricular fibrillation was known to have occurred at least six times, and paroxysmal tachycardia once. He suggested that these conditions are probably the functional consequence of the underlying cardiac disease (principally aortic regurgitation and atrial septal defects), and this explanation seems a reasonable one for most cases. Auricular fibrillation is a well-known complication of an atrial septal defect. In the case of cardiac failure referred to in the preceding paragraph (Whitfield, Arnott, and Stafford, 1951), in which no important abnormality other than 'myocarditis' was found at autopsy, auricular fibrillation occurred as a terminal event. Paroxysmal auricular tachycardia, with coarctation and aortic incompetence, occurred in Fischl and Ruthberg's (1951) patient referred to in the sec-

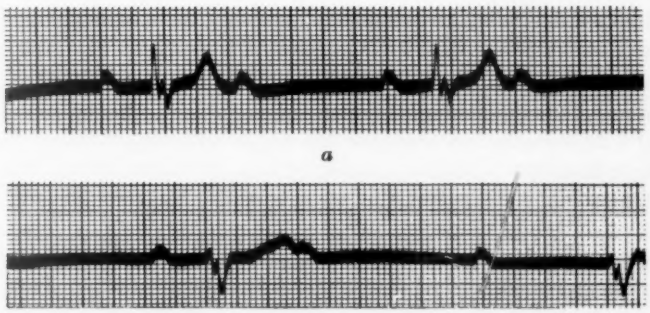
tions on myocarditis and on coarctation, and also in one undoubted case of the Marfan syndrome from the present series.

A woman aged 24 (Case 15, Table VI), with skeletal features of the Marfan syndrome, was admitted to hospital with attacks of paroxysmal supraventricular tachycardia (Fig. 4). Owing to the severe skeletal deformities present in the chest and spine it was difficult, from clinical and radiological examination, to make a precise anatomical diagnosis of the cardiac condition, but the principal finding was a basal systolic murmur and thrill. There was a past history of subacute bacterial endocarditis, for which she had been treated successfully. Unfortunately she died suddenly at home, and no autopsy was performed.

FIG. 4. Case 15.
Paroxysmal tachycardia.

Defects of Conduction

Reference to partial heart block, in the form of prolongation of the PR interval, was made by Baer, Taussig, and Oppenheimer (1943), and in one of the case records of the Massachusetts General Hospital (1950), but in neither was it sufficiently severe to result in dropped beats. Bundle branch block was present in one case of the Marfan syndrome, with aortic incompetence and dilatation of the aorta, reported by Marvel and Genovese in 1951, in one case reported by Strayhorn and Wells in 1947, and in 'several' cases with aortic incompetence referred to by McKusick in his review (1955*b*). In one patient from the present series impairment of conduction was more severe than in any previously recorded case.



a

b

FIG. 5. Case 16. (*a*) Partial (2:1) heart block in 1951.
(*b*) Complete heart block in 1955.

A man aged 38 (Case 16, Table VI) was first seen seven years previously on account of bradycardia, which was noted in a surgical ward, to which he had been admitted with a view to sympathectomy for severe acrocyanosis of the

hands and feet and ulceration of the lower third of each leg. The heart was not enlarged, and the aorta not dilated. An unimpressive grade II aortic systolic murmur was present, but no diastolic murmur. The blood-pressure was 220/90. An electrocardiogram (Fig. 5*a*) showed partial heart block, with a ventricular rate of 30 per minute. So far this man has been kept under observation for seven years. Two years after first examination he developed angina pectoris, which has been progressive. Four years after this complete heart block was noted (Fig. 5*b*), and the following year he had reverted to partial heart block. There has been no change in heart size or auscultatory findings. The precise cause for this defect of conduction remains obscure. The electrocardiogram shows no other changes suggesting myocardial ischaemia.

Atrial Septal Defects

The relationship between atrial septal defects and the Marfan syndrome is not yet clearly established. It was previously thought that arachnodactyly and atrial septal defect were commonly associated. The proven cases upon which this opinion was based are in fact few, amounting to three cases of atrial septal defect, and seven described as patency of the foramen ovale, some of which would not now be diagnosed as atrial septal defects. Much depends on the criteria used for the cardiological diagnosis and, as already mentioned, this is frequently inadequate. The proven cases of atrial septal defect in the Marfan syndrome are those reported by Bronson and Sutherland (1918), Piper and Irvine-Jones (1926), and McKusick (1955*b*). Patent foramen ovale was reported by Salle (1912), and by Börger (1914), and both authors gave atrial septal defect (in which they apparently include patent foramen ovale) as the usual cardiac manifestation associated with arachnodactyly. In other reported cases patent foramen ovale was associated with aortic aneurysms (Baer, Taussig, and Oppenheimer, 1943), aneurysmal dilatation of the aorta (Yettra and Lasky, 1947), and dissecting aneurysm (Oswald and Parkinson, 1949; Goyette and Palmer, 1953). In addition to these proven cases, there are a number of published instances of cases of the Marfan syndrome with possible or probable atrial septal defect. For example, Ellis (1940) described a child of four years with arachnodactyly who had a harsh systolic murmur in the fourth left intercostal space and a mid-diastolic murmur at the apex. It is also possible to consider this problem from the opposite standpoint, namely, the question of how many cases of known atrial septal defect have stigmata suggestive of the Marfan syndrome. In a series of 900 cases of congenital heart disease, Wood (1956) reported an incidence of atrial septal defect in 162 (18 per cent.). Of these 162 patients, one-quarter had arachnodactyly, high-arched palate, or a chest deformity usually of 'pigeon' type, in about equal proportions. Of Roesler's (1934) series of 62 cases, deformity of the thoracic skeleton was noted in 12. It seems at least possible that if the less obvious skeletal manifestations of the Marfan syndrome were looked for, and the family history more thoroughly studied, quite a large number of cases of atrial septal defect might come to be considered in this category.

Of the two patients reported here (Cases 17 and 18, Table VI) the first was a proven case of the Marfan syndrome. The second had an atrial septal defect in association with several skeletal features suggestive but not diagnostic of the syndrome, and illustrates the difficulty of deciding the limits of normality and the precise criteria for diagnosis.

A girl aged 10 (Case 17, Table VI) had had progressive dyspnoea on exertion since the age of four years. Clinical, radiographic, and electrocardiographic signs suggesting atrial septal defect were confirmed by cardiac catheterization and angiocardiography. She died suddenly from cardiac failure two years after the above examinations.

A man aged 21 (Case 18, Table VI) was referred for an opinion on account of a cardiac murmur. He had noticed mild dyspnoea on exertion for many years. Clinical, radiographic, and electrocardiographic signs of atrial septal defect were confirmed by catheterization, and the defect was repaired by operation.

Ventricular Septal Defect

In their review of 28 cases of cardiovascular complications in the Marfan syndrome examined post-mortem, Marvel and Genovese (1951) found no instance of ventricular septal defect. A number of cases have been reported with a clinical diagnosis of ventricular septal defect, for example, those of Cockayne (1935) and Giraud, Borea, Jayle, and Mockers (1938), but we have not found any unequivocal example of the Marfan syndrome in which the presence of such a defect was proved, and it may be that there is no special association between the two conditions.

Coarctation of the Aorta

Coarctation was present in two of the 28 post-mortem cases of the Marfan syndrome with cardiovascular complications reviewed by Marvel and Genovese (1951). A number of other instances, however, have been reported (Bronson and Sutherland, 1918; Uyeyama, Kondo, and Kamins, 1947; Fischl and Ruthberg, 1951) and, if the difficulty of diagnosing *formes frustes* of the syndrome is taken into account, the incidence may be significant. McKusick (1955*b*) referred to two cases of mild coarctation in men aged 40 and 24. In each there was evidence of the Marfan syndrome on other grounds; one also had dissecting aneurysm of the aorta. Published cases in which coarctation is described in association with other cardiovascular complications of the Marfan syndrome (especially aortic aneurysm or cystic medio-necrosis), though without mention of skeletal or ocular changes, include those of Harrison (1939), Davies and Fisher (1943), Smith and Targett (1897), and Wasastjerna (1903).

Patent Ductus Arteriosus

The first reported case of patent ductus arteriosus with the Marfan syndrome is usually quoted as that of Apert (1938). As Bingle (1957) has pointed out, this

is an error due to mistranslation. In the patient of Anderson and Pratt-Thomas (1953) (referred to above in the section on the pulmonary artery), who died from rupture of the artery secondary to medio-necrosis, there was also patency of the ductus arteriosus, and this seems to be the first authentic case. Lillian (1949) and Bingle (1957) have also reported cases. These three patients, together with the two referred to by McKusick (1955*b*), form a high proportion, considering the small number of reported cases of the Marfan syndrome with cardiovascular complications. This suggests, but does not prove, that patent ductus arteriosus is more common in patients with the Marfan syndrome than in the general population. There are also accounts in the literature of patent ductus in association with aortic cystic medio-necrosis (Caylor, 1918; Hall, 1926), but without mention of other features to suggest the Marfan syndrome.

Rheumatic Heart Disease

It has been suggested (Futcher and Southworth, 1938) that there is an increased liability to rheumatic endocarditis in the Marfan syndrome. The main evidence in favour of this view has been the number of cases reported with murmurs suggesting valvular heart disease and with pathological evidence of endocardial valvular changes. The evidence, however, of a specific connexion between the two conditions is tenuous. It seems probable that the systolic murmurs have been due either to myxomatous degeneration of the valves or, sometimes, to skeletal deformities of the chest. Rolled and thickened cusps, particularly of the mitral and aortic valves, were reported in 10 of the 28 cases in Marvel and Genovese's series (1951). Comment on this type of pathological change has been made by Salle (1912), Weill (1932), Giraud, Borea, Jayle, and Mockers (1938), Stewart (1939), Lillian (1949), Harrison (1939), Uyeyama, Kondo, and Kamins (1947), and Baer, Taussig, and Oppenheimer (1943). Tobin, Bay, and Humphreys (1947) ascribed the pathological changes in the thickened mitral valve cusps to cystic myxomatous degeneration. None of the pathological accounts describe rheumatic vegetations or the presence of Aschoff nodules. Most of them clearly distinguish the changes from those due to rheumatic fever.

As regards clinical evidence, a few patients have been described as having mitral stenosis or aortic incompetence, for example, by Vogt (1931), Burch (1936), and Green and Emerson (1943), although in most instances the clinical descriptions have been scanty. Cases reported by Reynolds (1950) and by Futcher and Southworth (1938) presented evidence of valvular disease, but it was not of rheumatic aetiology. In the great majority of cases in which reference is made to the heart the finding on auscultation has been that of a systolic murmur. Supporting clinical evidence of a rheumatic aetiology is noticeably lacking. Rheumatic nodules, pericarditis, and arthritis (except in the case reported by Futcher and Southworth (1938)) are not mentioned. Subacute bacterial endocarditis has been reported by Vivas-Salas and Sanson (1948) and McKusick (1955*b*) (each in one case), and was probably present in the case

reported by Olcott (1940) in which two friable, pale red, elevated masses were found on one cusp of the mitral valve.

Futcher and Southworth's (1938) original suggestion of a connexion between rheumatic carditis and the Marfan syndrome was based partly on the opinion of Roesler (1934) that there was a high incidence (nearly 50 per cent.) of chronic fibrotic lesions of the mitral valve in his series of 62 atrial septal defects, and on the fact that atrial septal defects were thought to be the commonest cardiac abnormality in the Marfan syndrome. These observations, however, have not been confirmed, and Reynolds (1950), in a good review of the literature, concluded that 'typical rheumatic endocarditis appears to be rare at necropsy compared with the number of possible but atypical cases'. The present series includes two unequivocal cases of mitral stenosis.

A woman aged 24 (Case 19, Table VI) had typical clinical, cardiographic, phonocardiographic, and electrocardiographic signs of rheumatic mitral stenosis and aortic incompetence with pulmonary hypertension. Mitral valvotomy was carried out successfully.

A man aged 19 (Case 20, Table VI) had had valvular heart disease discovered at the age of eight years, and progressive dyspnoea on exertion. He had typical physical, cardiographic, and electrocardiographic signs of mitral stenosis with slight incompetence. Mitral valvotomy was carried out successfully.

There is therefore no doubt that mitral stenosis, indistinguishable from that produced by rheumatic fever, may be found in patients with the Marfan syndrome. It seems that cardiac murmurs can far more often be attributed to myxomatous endocardial changes, and in no reported case has there been pathological evidence that mitral stenosis was produced by this process.

Praecordial Murmurs

It will be evident that praecordial murmurs in patients with the Marfan syndrome may have the characteristic features of some form of congenital heart disease. In other cases they can reasonably be attributed to endocardial changes in the aortic or mitral valves, such as are known often to be present. Sometimes they can be explained by gross skeletal deformities such as 'funnel' or 'pigeon' chest, or an extremely flattened chest, which again are known to be associated with such murmurs. Occasionally 'scratchy' sounds of extracardiac type may be heard, as in healthy people, but we have the impression that they are more frequent in the Marfan syndrome.

Dextroversion

The following case of dextroversion of the heart is considered worthy of inclusion because its occurrence has not previously been reported in patients with the Marfan syndrome. As with septal defects, coarctation of the aorta, and patent ductus arteriosus, the relationship is probably not a direct one, but only that of an associated congenital anomaly. Dextroversion is a form of

dextrocardia which results from congenital malrotation of the heart about its longitudinal axis. Early development is normal. At the sixth week of intrauterine life, when the heart is well differentiated and central in position, rotation to the left about its longitudinal axis normally occurs. If rotation occurs to the right, dextroversion results.

A man aged 21 (Case 21, Table VI) was referred by a National Service Board for a cardiological opinion. He had no relevant symptoms, and no abnormality as regards the heart was found on clinical examination or on electrocardiography, apart from the position of the apex beat, but radiography showed the characteristic contour of dextroversion (Plate 6, Fig. 22).

Eye

The ocular manifestations of the Marfan syndrome will not be discussed in any detail here. Full information is available in many papers in ophthalmological journals (Burch, 1936; Lloyd, 1948; Lutman and Neel, 1949; Rados, 1942). The classical anomaly which is almost diagnostic, although very occasionally present in other conditions, is that of ectopia lentis. As a result of laxity of the suspensory ligaments of the lens, secondary to degenerative changes, the lens become displaced. The condition is usually bilateral, and can be seen with the slit lamp. Tremulous irides (iridodonesis) may also be present from the same cause, and can be detected by getting the patient to look from side to side. Myopia is very commonly present. Other ocular abnormalities which may be present include detachment of the retina, blue sclerae, cloudiness of the cornea, iritis, glaucoma, small pupils, and poor mydriasis from hypoplasia of the dilator muscles.

Lungs

Congenital malformations of the lungs in patients with the Marfan syndrome have been noted on a number of occasions, and include two-lobed right lung (Börger, 1914), failure of division of the lobes of the lungs (Piper and Irvine-Jones, 1926), one-lobed left lung and a small right middle lobe (Green and Emerson, 1943), and congenital cystic disease (Lillian, 1949); but none seems to have been of any clinical significance. Oswald and Parkinson (1949) reported the case of a young man with recurrent spontaneous pneumothorax from congenital cystic disease, who died from rupture of a dissecting aneurysm, but did not mention any ocular or skeletal defects. There is no histological evidence as to whether the changes in the lungs are similar to those occurring in other tissues, and the defects appear to be in the nature of associated congenital anomalies, without direct relationship to the Marfan syndrome.

Genito-Urinary Tract

Congenital defects of the genito-urinary tract in patients reported to have the Marfan syndrome include genital hypoplasia (Börger, 1914; Delord and Vialle-

font, 1936), undescended testes (Haridas, 1941; Stern, 1944), ectopia testis (Olcott, 1940; Fischl and Ruthberg, 1951), polycystic kidneys (Booth, Loughridge, and Turner, 1957), and congenital ureteric stricture (Booth, Loughridge, and Turner, 1957). These conditions may be no more than associated congenital defects, but their occurrence is noteworthy, and there was one such case in our series.

A man aged 22 (Case 22, Table VI) was found to have polycystic kidneys, with one kidney in the pelvis, during routine investigations for the assessment of hypertension.

Discussion

Though not a common condition, the Marfan syndrome is by no means as rare as the published cases would suggest. The infrequency of its recognition, except in classical cases with arachnodactyly and ectopia lentis, is due to the fact that no absolute criteria are available for making the diagnosis, particularly in the skeletal system. The skeletal defects are often difficult to recognize when they do not occur in a severe form. This is because they represent extremes of the normal distribution curve for biological variables in the population, and the point at which abnormality should be accepted is clearly an arbitrary one. The manifestations considered to be of importance for the diagnosis are certain abnormal skeletal measurements, arachnodactyly, 'funnel' or 'pigeon' deformity of the chest, abnormal mobility of joints, high patellae, vertebral deformities, talipes equinovarus, dolichocephaly, and high palate. Others which have been quoted in the literature, but which we consider of little importance, are prognathism, frontal bossing, prominent ears, and spina bifida. The cardiovascular defects may be grouped into those which may be true manifestations of the syndrome, such as aortic and pulmonary artery defects, myocarditis, arrhythmias, and heart block, and those which, though occurring in the syndrome with some frequency, are probably merely associated congenital faults. The latter group includes septal defects and coarctation of the aorta. The first group constitutes serious and often lethal conditions which it is important to recognize, though in general they are untreatable.

The genetic basis for the Marfan syndrome is still uncertain. There is a strong family history in some instances, but sporadic cases are frequent. Ocular, skeletal, and cardiac anomalies may occur together or independently, and the range of abnormality in each is very wide, most cases occupying an intermediate position. The published cases suggest a range from *formes frustes* to extreme examples. If the genetic abnormality appears in a person of asthenic build the 'typical Marfan' appearance results, but if in one of pyknic type the results are less obvious, and may be masked. Patients with severe forms of the disease are unlikely to survive and reproduce their kind, and so natural selection favours the appearance of milder forms. As in other inherited disorders, 'sporadic' cases tend to be more severe. Lutman and Neel (1949), in a paper on genetic aspects, concluded that 'the balance of evidence would seem to favour a single,

dominant, autosomal, pleiotrophic factor, the effects of which are sensitive to modification by other inherited genetic modifiers and perhaps factors in the early environment'. Those interested in the genetic aspects of the Marfan syndrome should read this paper and that of Rados (1942). Both give many references to the relevant literature.

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Summary

The skeletal and cardiovascular manifestations of the Marfan syndrome are described in 40 patients, of whom 14 had both skeletal and cardiovascular changes.

The place of body measurements in the diagnosis of the syndrome is discussed in relation to available figures for the normal population.

An index of arachnodactyly based on the hand radiograph has been devised, and a level of significance suggested.

The relative importance of the skeletal manifestations, and the frequency with which symptoms due to the syndrome are unrecognized as such, are discussed.

The cardiovascular anomalies which have been reported in association with skeletal or ocular manifestations of the syndrome are reviewed, and illustrated from personal experience.

Dilatation of the aortic valve ring, the sinuses of Valsalva, the aortic arch, or descending aorta, or rupture of the aorta with or without a dissecting aneurysm, may result from medio-necrosis.

Dilatation of the pulmonary artery may also result from medio-necrosis.

Deformities of the valve cusps, with cardiac murmurs, may result from myxomatous degeneration.

Myocarditis, defects of conduction, and cardiac arrhythmia may occur, but the pathogenesis is obscure.

Rheumatic heart disease may occur, but more often valvular defects result from myxomatous degeneration.

Congenital heart disease in the form of atrial septal defect, coarctation of the aorta, and patent ductus arteriosus, may be present, and are probably associated congenital defects rather than aetiologically part of the syndrome.

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FIG. 6. Case 1. Scoliosis of the lumbar spine; sclerosis of the sacro-iliac joints

FIG. 7. Case 3. Posterior slipping of vertebra L2 on L3, with osteophytic outgrowths

FIG. 8. Case 4. Arachnodactyly; overmobility of the joints and dislocation of the right thumb

FIG. 9. Case 4. Arachnodactyly

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FIG. 6. Case 1. Scoliosis of the lumbar spine; sclerosis of the sacro-iliac joints

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FIG. 9. Case 4. Arachnodactyly

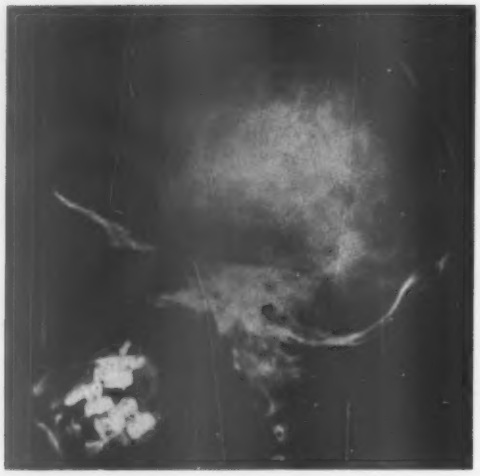


FIG. 10. Case 5. Dolichocephaly

FIG. 11. Case 6. High patellae

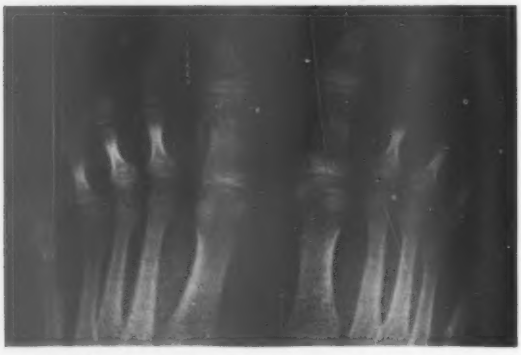


FIG. 12. Case 7. Deformities of the distal phalanges

FIG. 13. Case 8. Congenital fusion of the second and third cervical vertebrae

FIG. 14. Case 9. Gross deformity of the femoral heads

FIG. 15. Case 15. Funnel deformity of the sternum

FIG. 16. Case 17. Pseudo club feet

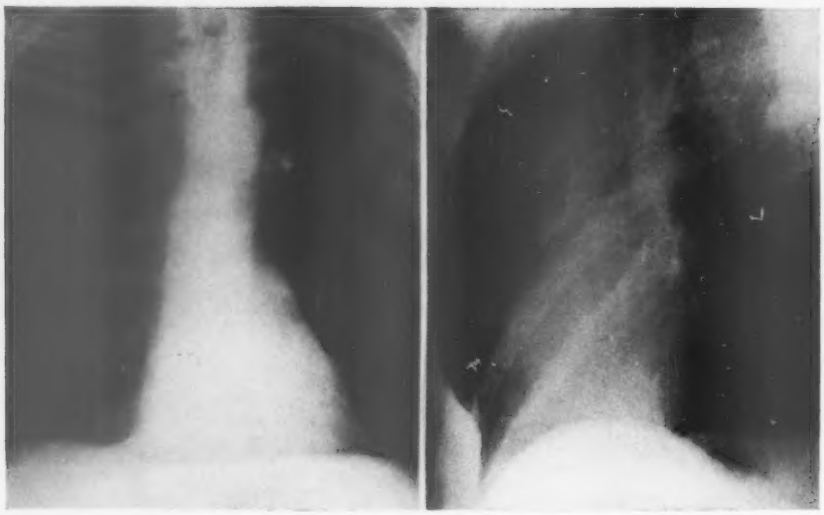


FIG. 17. Case 3. Dilatation of the ascending aorta

FIG. 18. Case 11. Aneurysmal dilatation of the ascending and descending arch of the aorta

FIG. 19. Case 13. Thickened margins of the aortic cusps, with smooth nodular swellings and fenestration

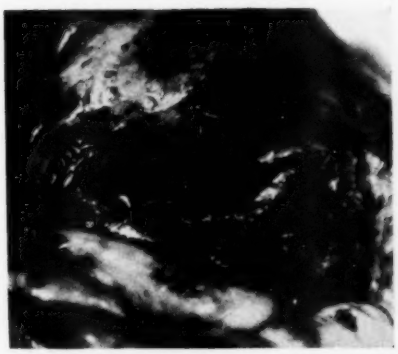
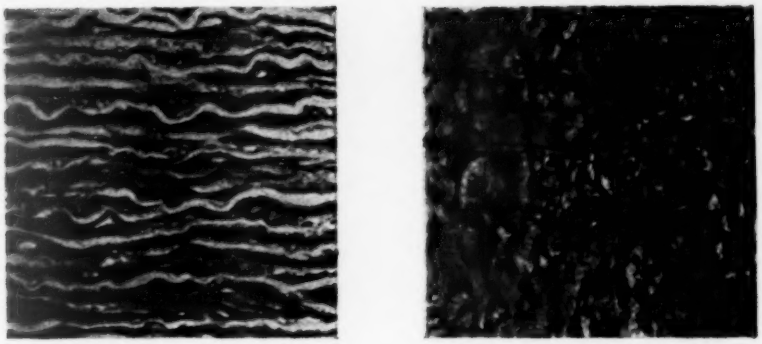


FIG. 20. Case 13. Transverse tear through the aortic wall

FIG. 21. Case 14. Aneurysmal dilatation of the pulmonary artery

FIG. 22. Case 21. Dextroversion



a *b*

FIG. 23. Longitudinal sections of aortic media (thionine stain)
(*a*) Normal. The pink-staining material is normal ground-substance
(*b*) Medial degeneration in a case of the Marfan syndrome, showing excess of ground-substance

616.46–006.441

HODGKIN'S DISEASE WITH AND WITHOUT ALCOHOL-INDUCED PAIN[1]

A Clinical and Histological Comparison

By A. H. JAMES

(From the Medical Unit, Cardiff Royal Infirmary)

With Plate 8

Some patients with Hodgkin's disease experience pain after they take alcohol. Not until 1950 was this symptom first mentioned, by Hoster; since then 58 instances of it have been described (Table I). Such pain has occurred after almost all kinds of alcoholic drink, and also after intravenous injection of ethyl alcohol, suitably diluted. The patient of Hall and Olson (1955) developed severe pain while he was being given 5 per cent. ethyl alcohol intravenously as a palliative. Alcozer and Azzena (1955) and Trimarco (1957) were able to reproduce the pain by giving alcohol intravenously. Kühböck and Reimer (1957) could sometimes do so, but Sándor (1955) failed to reproduce it in two patients. The interval between drinking and the onset of pain is usually short; many accounts say that the pain is immediate. Where an interval is specified it is usually between five and 15 minutes. Exceptional experiences are those of Greiner, Brenner and Hambalgo (1956), in whose patient the interval was 30 minutes, and of Kühböck and Reimer (1957), who recorded intervals of 45 minutes to several hours. The pain may last for only 10 minutes, or it may go on for several hours, even leaving a residual soreness next day. It is usually severe, and may reduce the patient to tears, requiring opiates for its relief. Sometimes, however, only slight pain is caused.

The pain is felt in at least one of the sites of the disease. Retrosternal pain is common where mediastinal nodes are involved, while with axillary or cervical nodes pain is felt in the shoulder, neck, and arm. The abdomen and groin are common sites, and pain in the back, which may or may not pass down the leg, has often been described. When disease is present at several sites, pain may not be felt in all of them. When two diseased areas are close together, such as the neck and axilla, it may be difficult to say whether pain is arising from one or both. Examples have been recorded, however, of pain occurring simultaneously at more than one site; for instance, a patient of Conn (1957; Case 3) had pain in the neck, axilla, and groin. On the other hand, pain may be present at only one site when disease is widespread; Petch's (1953) patient had pain after

[1] Received March 9, 1959.

drinking only in the hypogastrium, although there were diseased nodes in the neck, one of which was subjected to biopsy. Some patients have pain apart from that caused by alcohol. In such cases alcohol may aggravate pain already present, or it may produce pain at a different site. In patients who have disease at successive sites, treated in sequence, alcohol-induced pain may or may not appear at each site of recurrence. One patient (Case 8) of the present series had had treatment for nodes in the axillae, neck, and groins over a period of five years before he started to have alcohol-induced pain in abdominal nodes: he was a heavy drinker throughout. Successful treatment abolishes alcohol-induced pain; one patient of de Winter (1953; Case 1) had had very severe pain in the region of the coccyx, where there was erosion of bone. After two weeks of radiotherapy alcohol caused only slight pain, and none after three.

TABLE I

Reported Instances of Alcohol-induced Pain in Hodgkin's Disease

Authors	*Number of Cases*
de Backer and Verbeke (1952)	1
Verbeeten (1952)	4
Anonymous (1952)	1
Justin-Besançon, Lamotte-Barillon, and Debray (1952)	2
Gros, Veillon, and Waeckel (1953)	3
de Winter (1953)	2
Crowley (1953)	1
Bichel and Bastrup-Madsen (1953)	9
Petch (1953)	1
Battistini and Bellomo (1954)	2
Alcozer and Azzena (1955)	3
Sándor (1955)	3
Hall and Olson (1955)	1
Albahary (1956)	1
Schwartz (1956)	2
Greiner, Brenner, and Hambalgo (1956)	1
Godden, Clagett, and Andersen (1956)	4
Conn (1957)	3
Trimarco (1957)	5
Kühböck and Reimer (1957)	5
Braun and Shnider (1958)	2
Tweeddale, Whelan, and Browning (1958)	2
Total	58

Hodgkin's disease is the only condition in which this symptom has been recorded in any substantial number of cases. It has been less assiduously sought, however, in other diseases. Alexander (1953) mentioned its occurrence in two cases of osteomyelitis. James, Harley, Horton, and Storring (1957) described two patients with carcinoma, arising probably in the thymus and in the pancreas respectively, who had alcohol-induced pain. Conn (1957) found one patient with alcohol-induced pain among six with osteomyelitis, and one among three with fractures of bone; he also found the symptom in a patient with pyogenic lymphadenitis. Braun and Shnider (1958) tested four patients with osteomyelitis, and found one with alcohol-induced pain; of five patients with fractures two had alcohol-induced pain. Among 12 patients with malignant

lesions in different sites one, who had carcinoma of the breast and an axillary node invaded by 'an inflammatory malignant process', felt very brief pain in this node one minute after taking alcohol. Apart from these cases, the symptom has been found only in Hodgkin's disease, despite a search for it among patients with lymphomatous, leukaemic, and neoplastic conditions by Battistini and Bellomo (1954), Alcozer and Azzena (1955), and Conn (1957). The figures just quoted suggest, however, that a similar search among patients with osseous lesions would reveal alcohol-induced pain in a substantial proportion.

TABLE II

Frequency of Alcohol-induced Pain in Hodgkin's Disease

Authors	*Number of patients tested*	*Positive*
Bichel and Bastrup-Madsen (1953)	62	9
Battistini and Bellomo (1954)	14	1
Alcozer and Azzena (1955)	18	3
Sándor (1955)	15	5
Conn (1957)	10	3
Trimarco (1957)	23	5
Kühböck and Reimer (1957)	30	5
Braun and Shnider (1958)	9	2
Present author	24	2
Total	205	35

A clinical impression that this symptom is rare in Hodgkin's disease may be misleading. A patient may never have taken alcohol, but yet, on testing, be found to have the symptom. The relation of pain to drinking may not have been noticed by the patient, or may not be mentioned because it seems bizarre. The only reliable estimates of the frequency of alcohol-induced pain are those made after a regular inquiry in a consecutive series, and after observation of the effect of administration of alcohol. Nine series have been examined in this way, with the results shown in Table II; the combined incidence is 35 in 205, or 17·1 per cent. The variation in incidence found by different authors is not too great to have occurred by chance. Five patients with Hodgkin's disease out of six, therefore, are not liable to alcohol-induced pain; the cause of this difference might be revealed by a comparison of patients with Hodgkin's disease with and without alcohol-induced pain. The present paper reports the results of such a comparison.

Patients Studied and Methods

Twenty-four patients with Hodgkin's disease who had been admitted to the Cardiff Royal Infirmary or the Cardiff Radiotherapy Centre, either at their first presentation or during relapse, were asked about alcohol-induced pain. Two patients, one man and one woman, gave a clear history of such pain. Twenty of the remaining 22 constitute the control series, and will here be called 'alcohol-negative'. All but four of these 20 patients were tested with alcohol before

treatment. Fifteen were given 10 ml. of ethyl alcohol in orange juice by mouth, and one was given 20 ml. of 20 per cent. ethyl alcohol intravenously. None had pain when so tested. The four patients who were not tested with alcohol had drunk alcohol regularly without pain at a time when their disease was active.

Of the 13 patients with alcohol-induced pain ('alcohol-positive'), two were discovered in the above-mentioned inquiry; one was a patient of Dr. R. J. K. Brown (to be published); five were patients of Dr. A. M. Jelliffe; two were patients of Dr. J. de Winter (de Winter, 1953); one was a patient of Dr. C. P. Petch (Petch, 1953); and two were patients of Dr. D. Crowley (one reported by Crowley, 1953). Brief histories of those patients neither previously reported nor to be reported are appended to this paper.

TABLE III

Site of Biopsy

	Neck	*Axilla*	*Groin*	*Epitrochlear*	*Unrecorded*
Alcohol-positive	9	2	1	0	1
Alcohol-negative	10	1	3	2	4

Histological material. In all patients the diagnosis had been confirmed by biopsy of a lymph-node; the sites of biopsy are given in Table III. Three patients had had two biopsies each; one of these was alcohol-negative, and two alcohol-positive. One alcohol-negative patient had had a biopsy and subsequently a block dissection.

Histological comparison. The sections were examined independently by three pathologists, namely Dr. A. G. Heppleston, Dr. H. J. Whiteley, and Dr. W. Jones Williams. They made the assessments on which the histological comparison is based, but the author alone is responsible for the subsequent treatment of the data and for the conclusions. It was agreed beforehand that they would give a score of 0 to 4 for each section in respect of the prominence of the following features:

Reticulum cells, including Sternberg-Reed giant cells.
Mitoses in reticulum cells.
Neutrophile polymorphs.
Eosinophils.
Plasma cells.
Fibrosis and fibroblasts.
Necrosis.

The pathologists were told that the sections had all been diagnosed as showing Hodgkin's disease, and none of them dissented from this diagnosis in any of the cases. They also knew that some of the sections were from patients who had had alcohol-induced pain, but not the proportion of patients who had had such pain. Code numbers were allotted at random to the whole series, and duplicate biopsies were coded as if they were separate cases.

Clinical comparison was based on the case notes made up to the time of biopsy, and before any treatment had been given. The notes of one alcohol-negative

patient could not be traced, and there were occasional items among the others about which information was lacking.

Results

Histological comparison. The scores returned by each pathologist have been added to make a total score for each feature, with a possible range of 0 to 12. Where two biopsy specimens were examined, the mean of the scores has been taken. Table IV gives the mean score for each feature for the positive and negative groups, the standard errors of the means, and, for those differences which are significant, the degree of such significance. Three of the seven features

TABLE IV

Mean of the Total Histological Scores for each Feature and for each Series

	Mean total score		*Standard error*		
	Positive	*Negative*	*Positive*	*Negative*	*P*
Reticulum cells	7·54	8·32	0·45	0·40	
Mitoses	2·37	3·75	0·39	0·39	<0·02
Neutrophils	5·54	3·92	0·96	0·60	
Eosinophils	7·85	3·95	0·68	0·62	<0·001
Plasma cells	4·42	3·37	0·58	0·34	
Fibrosis	7·97	4·32	0·76	0·48	<0·001
Necrosis	1·69	1·40	0·46	0·50	

TABLE V

Ratios of Mean Scores for Positive Series to Mean Scores for Negative Series as found by each Pathologist

Reticulum cells	0·82	0·87	0·91
Mitoses	0·59	0·65	0·64
Neutrophils	1·75	1·57	1·25
Eosinophils	2·18	1·65	2·08
Plasma cells	1·46	2·36	0·95
Fibrosis	1·87	2·16	1·49
Necrosis	1·28	0·57	1·33

show significant differences, the alcohol-positive group having lower scores for reticulum-cell mitoses and higher scores for eosinophils and fibrosis. In the case of necrosis the scores are low, and the average for the negative group depends largely upon a single high figure. In four out of 13 alcohol-positive cases, and in three out of 20 alcohol-negative, the total score for necrosis exceeded 2: this difference is insignificant. Table V reveals the extent of the agreement between the three pathologists, showing the ratio of the mean score for the positive series to that for the negative. Only for plasma cells and necrosis were the ratios of any two pathologists on opposite sides of unity; in necrosis the scores were too low for this ratio to have much significance. One pathologist found a marked difference in plasma cells between the two groups, but the combined scores are not significantly different. (The sections had not been specially stained to show plasma cells.) These exceptions apart, the main conclusions

are supported by all three pathologists. Table VI shows the total scores for each feature for those cases in which specimens of tissue were available from biopsies taken on different occasions. The two alcohol-positive patients who had a second biopsy both had it for the same reason, namely that the disease was at first thought to be an inflammatory one. In both patients Hodgkin's disease was confidently diagnosed on the second biopsy, and amply confirmed by their further course.

TABLE VI

Histological Scores in the Four Patients who had Two Biopsies

	Alcohol-positive				*Alcohol-negative*			
Interval in days between biopsies	26		30		13		52	
Biopsy	I	II	I	II	I	II	I	II
Reticulum cells	7	5	7	5	9	7	10	9
Mitoses	1	2	2	1	4	3	5	6
Neutrophils	7	8	7	8	2	2	3	2
Eosinophils	6	3	12	6	5	0	3	2
Plasma cells	5	3	5	8	4	2	4	3
Fibrosis	4	4	11	12	2	5	5	7
Necrosis	0	2	0	4	0	0	2	0

The alcohol-negative patients tended to be older than the alcohol-positive. The difference might have arisen by chance ($t = 1{\cdot}34$; $0{\cdot}2>P>0{\cdot}1$), and the manner in which the cases were collected provided opportunities for bias. It is, however, necessary to show that this difference did not account for the histological differences between the groups. Inspection of scatter diagrams suggested that there might be some negative correlation of eosinophil score with age, and possibly some positive correlation of mitosis score with age. Table VII shows

TABLE VII

Significance of the Differences between Histological Scores for Positive and Negative Groups (Both Sexes) after Correction of the Effect of Age on Scores by Analysis of Covariance

	t	P
Eosinophils	3·79	<0·001
Fibrosis	3·77	<0·001
Mitoses	2·05	0·05

the values of t for the differences between histological scores for the positive and those for the negative groups, after correction by analysis of covariance for any linear effect of age on score. The differences for eosinophils and fibrosis are still very significant, but when age is taken into account the difference between the scores for mitoses is only just significant.

The positive group contained seven men and six women, the negative group 15 men and five women. More will be said later about the possible importance of this difference in sex ratio, but it is not too great to have occurred by chance ($\chi^2_c=0{\cdot}8$, $0{\cdot}3<P<0{\cdot}5$). As in the case of age, however, an unequal distribution, whether due to chance, to bias, or to a real difference of distribution,

may have affected the difference in histological scores. Fig. 1 shows the scores for eosinophils, fibrosis, and mitoses plotted against age for each sex. The number of women is too small for any certain conclusion to be drawn, but the differences between the two groups as regards scores for fibrosis and for mitoses are much less apparent in the women. Table VIII gives the values of t for the histological differences separately for men and women, after correction by analysis of covariance for any linear effect of age on score. For the men, all the differences are significant, and it is noteworthy that removal of the women greatly increases the significance of the difference in mitosis scores. In the case of the women the scores for fibrosis and mitoses are not significantly different, and the scores for eosinophils barely so.

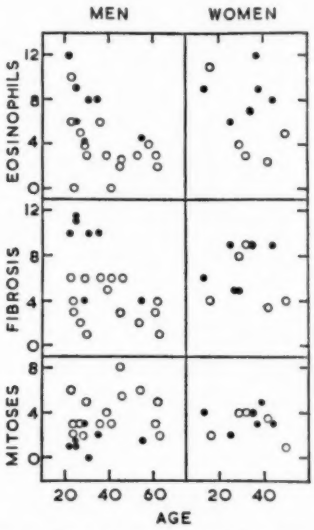


FIG. 1. The six scatter diagrams show the relationships between age on the one hand and scores for eosinophils, fibrosis, and reticulum-cell mitoses on the other, separately for men and women. The black dots represent cases with, the open circles cases without, alcohol-induced pain.

It has been noted in the introduction that alcohol-induced pain is not always felt in all diseased areas, and may therefore not have been felt in a node removed for biopsy. This was so in eight of the 13 alcohol-positive cases in the present series. Table IX shows the mean scores for these eight as compared with those for the other five; the histological features characteristic of the whole positive group are as conspicuous in the nodes in which pain was not felt as in those in which it was. More often than not fibrosis was macroscopically obvious in sections from patients with alcohol-induced pain. Plate 8, Fig. 3 shows such a section contrasted with one from the alcohol-negative group.

Clinical comparison. The comparison has been made between the clinical pictures at the time of biopsy; later in the evolution of the disease several patients in the control group came to exhibit features here listed as commoner in the alcohol-positive group. The peculiarity of the latter was that they showed

TABLE VIII

Significance of the Differences between Mean Histological Scores for the Positive and Negative Groups for each Sex. The Effect of Age on Score has been Corrected by Analysis of Covariance

Men

	Mean score			
	Positive	*Negative*	*t*	*P*
Eosinophils	7·21	3·57	2·68	<0·02
Fibrosis	8·64	3·87	3·42	<0·01
Mitoses	1·43	4·03	3·19	<0·01

Women

	Mean score			
	Positive	*Negative*	*t*	*P*
Eosinophils	8·50	5·10	2·36	<0·05
Fibrosis	7·17	5·70	0·97	0·3–0·4
Mitoses	3·50	2·90	0·75	0·4–0·5

TABLE IX

Mean Total Scores for Cases in the Positive Group with and without Alcohol-induced Pain in the Node taken for Biopsy, and for Cases in the Negative Group

	Positive		
	With	*Without*	*Negative*
Reticulum cells	8·60	6·88	8·32
Mitoses	3·00	2·00	3·75
Neutrophils	6·20	5·10	3·92
Eosinophils	7·60	8·06	3·95
Plasma cells	5·00	4·10	3·37
Fibrosis	8·00	7·94	4·32
Necrosis	1·80	1·62	1·40

these features often at an early stage. The mean age of the patients in the positive group was 31·8 years, and of those in the negative group 38·1 years. Symptoms had been present for an average period of 11 months in the positive group and 11·1 months in the negative group before the biopsy was done. This study has not provided any information about relative prognosis. Only three patients of the positive group and five of the negative are known to have died, the mean survival from the onset of the disease to death being 44 and 70 months respectively; this difference is insignificant owing to the large scatter. Comparison of the periods for which the living patients have survived hitherto is useless, because of the arbitrary way in which the patients have been selected.

The remainder of the clinical data are set out in Table X. The conclusions from Table X may be summarized as follows: (1) The two groups do not differ in respect of the proportion which showed constitutional disturbance (as defined at the foot of the Table), itching, variation in size, or tenderness, of the nodes, involvement of the neck, axillae, or groins, enlarged abdominal nodes, enlargement of the liver or spleen, fever, or anaemia. (2) The alcohol-positive group contains a significantly greater proportion of cases showing spontaneous pain in diseased areas, enlarged hilar or paratracheal nodes, and leucocytosis. These last three features will now be considered in detail.

TABLE X

Incidence of Clinical Features in each Group

	Positive			*Negative*			
Significant	*Present*	*Absent*	*Doubtful*	*Present*	*Absent*	*Doubtful*	*P*
Spontaneous pain	8	5	..	2	17	..	<0·01
Mediastinal nodes	9	3	1	2	13	4	<0·01
Leucocytosis (>11,000/cu. mm.)	10	3	..	3	15	..	<0·01
Insignificant							
Constitutional disturbance (see note 4)	7	5	..	6	10	..	..
Itching	2	10	..	3	13	..	..
Variation in nodes	5	7	..	8	11	..	..
Tenderness of nodes	4	9	..	4	14	..	..
Nodes in neck	11	2	..	15	4	..	..
,, axillae	9	4	..	10	8	1	..
,, groin	4	9	..	6	13	..	..
,, abdomen	2	10	1	0	19	..	..
Hepatomegaly and/or splenomegaly	4	9	..	4	15	..	..
Fever (>99·5° F.)	5	7	..	3	15	..	..
Anaemia (haemoglobin <75%)	3	9	..	3	14	..	..

NOTES: 1. A case has been entered as 'doubtful' if the notes express uncertainty in the mind of the clinician or radiologist as to the presence of a physical sign.

2. Values of χ^2_c have been calculated for the distribution of each feature as between positive and negative cases. Doubtful cases have been excluded. Significance is given only for those features in which it is high. In none of the other features did the difference in distribution approach significance.

3. If no information was available on a point, that case was excluded from the Table for that feature. Because of such exclusions the total number of cases under the headings 'positive' and 'negative' may be less than the full numbers 13 and 20 respectively.

4. Patients were assessed as having constitutional disturbance if the notes recorded the presence of at least two of the following: tiredness, loss of appetite, loss of weight.

Spontaneous pain. Eight of the 13 patients with alcohol-induced pain also experienced pain apart from drinking. In four of these eight the spontaneous pain was felt at the same site as that induced by alcohol, although there might be spontaneous pain at other sites as well. In the other four the two pains were in different places. Spontaneous pain was never severe, but it might keep the patient awake. Only two of the 12 alcohol-negative patients regarding whom information was available had spontaneous pain.

Mediastinal involvement. A report on a radiograph of the chest taken before

biopsy was available in all 13 patients of the positive group, and in 19 of the negative group. In one of the former and four of the latter doubt was expressed as to whether the mediastinal shadow was normal. Excluding these five, only two of the negative group showed definite enlargement of the mediastinal shadow, in contrast to nine of the smaller positive group. Four of these nine had alcohol-induced pain in the chest, although in one it appeared only at a later stage of the disease. In the other five the alcohol-induced pain occurred elsewhere. In four patients of the positive, and in none of the negative group, there were radiological changes in the lung fields. In one there was bilateral pulmonary infiltration, and in one a shadow in the right lower zone; in the other two there were large opacities in the upper zones, on the right in one case and on the left in the other. These opacities could not be distinguished from the mediastinal shadows, and may therefore have represented large mediastinal tumours rather than intrapulmonary disease.

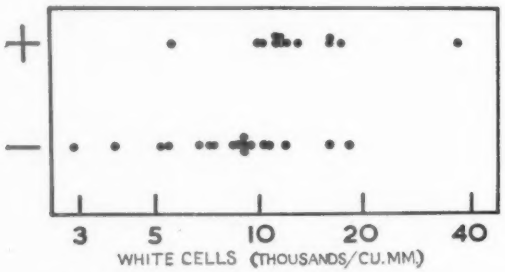


FIG. 2. The total white-cell counts of the patients with (+) and without (−) alcohol-induced pain. The scale is logarithmic.

White-cell count. Fig. 2 shows the distributions of the total white-cell counts in the two groups. The only patient with a leucopenia was in the alcohol-negative group; one patient with alcohol-induced pain had a count of 38,700 per cu. mm. Three of the negative group had a leucocytosis (18,200, 16,200, and 12,000 per cu. mm.). These patients had scores for eosinophils and fibrosis near the averages for the negative group, except that one had a rather high score for fibrosis. Similarly, the three alcohol-positive patients who were exceptional in having a normal white-cell count (5,600, 10,000, and 10,300 per cu. mm.) had the high scores for eosinophils and fibrosis characteristic of their group. The differential counts showed that, in both groups, any increase in white cells was nearly always in the neutrophile polymorph count. Only two patients had an eosinophilia; one was alcohol-negative, and had 15 per cent. of eosinophils in a total count of 9,000 per cu. mm.; she also had chronic bronchial asthma. One man with alcohol-induced pain had 12 per cent. of eosinophils in a total count of 11,300 per cu. mm. Otherwise percentages of eosinophils were small. There seemed to be little correlation between the number of white cells of each variety in the blood and in the diseased lymph-nodes; in the positive group generally, an increase of eosinophils in the nodes was accompanied by an

excess of polymorphs in the blood. An exception was a woman who had alcohol-induced pain, whose white-cell count was 38,700 per cu. mm.; 88 per cent. were polymorphs, and the lymph-node taken for biopsy was densely infiltrated with polymorphs, and was given the maximum score for this feature.

Discussion

The possibility that the observed differences were due to bias must first be considered. The two groups of cases were drawn from different sources; this circumstance, rather than any tendency for alcohol-induced pain to afflict patients of particular age or sex, may perhaps have led to the differences in age and sex distribution between the groups. These differences have already been shown not to have been responsible for the histological contrasts which have been found. As to the clinical differences, they are apparent in each sex considered separately, and there is thus no evidence that they arise from the different distribution of the sexes between the positive and negative groups. In general, however, the sub-groups are too small for the clinical differences to be significant for each sex alone. The clinical differences are also apparent when the groups are made comparable with respect to age by excluding all patients over the age of 40.

The control or alcohol-negative group was drawn from South Wales; of the 13 patients with alcohol-induced pain, 10 lived in London and the Home Counties, and only three in South Wales. If the observed differences were due to this difference of origin, the three non-Londoners among the positives should tend to resemble the negative group. This, on the whole, they do not do. Their scores for eosinophils and fibrosis are well up to the average for the positive group; two of the three had mediastinal involvement, and two of the three had a leucocytosis. Only in respect of spontaneous pain do these three tend to be exceptional among the positives; none had spontaneous pain, while only two of the other positive patients failed to have it. It could therefore be objected that the rarity of spontaneous pain among the control patients was due to their coming from South Wales, and that it was not otherwise associated with the absence of alcohol-induced pain. This seems exceedingly unlikely.

In making the histological comparison the pathologists had no way of separating the slides from positive and negative cases. They may perhaps have been biased in assessing one feature by knowledge of the prominence of another, but it is difficult to see how this could have been avoided.

Coming to the clinical analysis, one might argue that a more complete history might have been obtained from patients who described alcohol-induced pain, so that, for example, a history of spontaneous pain might have been elicited more often in such cases. This particular contention can be refuted. In seven of the alcohol-positive patients alcohol-induced pain had not yet occurred at the time that the symptoms were first recorded; yet five of these seven were noted to have spontaneous pain.

With minor reservations, therefore, artificial bias can be excluded as a cause

of the differences observed. The study thus leads to the conclusion that patients with Hodgkin's disease who, at some time or other in the course of their illness, suffer from alcohol-induced pain, differ from those who do not in the following respects:

1. They more often have, at an early stage of the disease, (1) spontaneous pain in one or more diseased areas; (2) a leucocytosis; (3) mediastinal involvement.

2. Sections from diseased lymph-nodes tend to show (1) fewer reticulum-cell mitoses; (2) more eosinophils; (3) more fibrosis.

Some support is to be found for these conclusions in previous reports. Most of the case reports are brief, and centre on the alcohol-induced pain itself. Other symptoms may be mentioned, but their absence from a particular report does not entitle one to infer that they were absent in reality. Eighteen of the 41 published descriptions, however brief, mention spontaneous as well as alcohol-induced pain. This frequency (44 per cent.) is not significantly different from that found in the present series, especially if allowance is made for the possibility that pain was sometimes present and not mentioned. Seventeen of the published case reports (excluding the four which form part of the present series) mention a chest radiograph at the time of biopsy. Fifteen of these showed enlarged mediastinal nodes. Of the two patients whose radiographs showed none, one developed enlargement of the hilar nodes six months later (Case 1 of Bichel and Bastrup-Madsen, 1953) and one had retrosternal alcohol-induced pain, suggesting that he had mediastinal disease not radiologically detectable (Case 9 of Bichel and Bastrup-Madsen). A further five, in whom a chest radiograph is not mentioned, had alcohol-induced pain in the chest at the onset. In 23 cases there is no mention of a chest radiograph, and there was no chest pain at the time of biopsy. In summary, there was, at the time of biopsy, evidence of mediastinal disease in 21 cases. In one there was evidence that there was no mediastinal disease (although such disease appeared six months later), and in 23 there was no evidence on the point. This confirms the fact that alcohol-induced pain is strongly correlated with early mediastinal involvement.

There are hardly any previously recorded data with which the present findings concerning total white-cell count and histology may be compared. White-cell counts are given in only two of the reported cases: in Godden, Clagett, and Andersen's (1956) Case 4 the figure was 26,000, and in Schwartz's (1956) Case 1, 12,000 per cu. mm. A normal white-cell count is much more likely to go unrecorded. The sections from Case 1 of Tweeddale, Whelan, and Browning (1958) were at first thought to show 'proliferative inflammatory glandular hyperplasia'; the diagnosis was later altered to Hodgkin's disease. Their second patient had Hodgkin granuloma. Godden, Clagett, and Andersen described three of their four patients as having 'Hodgkin's disease of a granulomatous type'. They discussed the possibility that alcohol-induced pain is produced by liberation of histamine from eosinophils, but noted that eosinophils were not conspicuous in sections from their patients. De Backer and Verbeke (1952) found little granulomatous tissue in sections from their patient, who was diagnosed as having 'paragranuloma of Hodgkin'.

An association between two events implies that either may cause the other, or that both are associated with a third. Applying this principle to the present case, one may consider the following possibilities:

1. Alcohol-induced pain, a peculiarity of some patients with Hodgkin's disease, gives rise to the clinical differences described, and to eosinophilic infiltration of the nodes and fibrosis.

2. In some patients with Hodgkin's disease the involved nodes are infiltrated with eosinophils and fibrotic; this leads to a number of clinical consequences, alcohol-induced pain being one.

3. Hodgkin's disease includes two distinct entities, characterized by somewhat different clinical and histological features; alcohol-induced pain occurs in only one of them.

These possibilities are not mutually exclusive; various interrelations may exist between the three clinical and three histological differences.

Could alcohol-induced pain have caused the peculiarities found in the patients who had the symptom? It is conceivable that whatever process takes place in the tissues during alcohol-induced pain could cause eosinophilic infiltration and lead to fibrosis. No observations have been made of the clinical appearance of lymph-nodes in which alcohol-induced pain is occurring. Gros, Veillon, and Waeckel (1953) spoke of *gonflement passager* accompanying the pain. Alcozer and Azzena (1955) described alcohol-induced pain in an ulcerated lesion on the front of the chest, biopsy of which had shown Hodgkin's disease. They did not comment on any change in the appearance of the ulcer during the attack of pain. Two examples are recorded of alcohol producing prolonged malaise in Hodgkin's disease. Hall and Olson (1955) said: 'one of our patients, a man who did not experience pain from alcohol, repeatedly observed an increase in the size of peripheral lymph nodes and fever after one night of heavy drinking and inadequate sleep.' One of Conn's (1957) patients with Hodgkin's disease 'described a generalised aching and feeling of ill health which lasted 12 to 36 hours after one or two drinks of beer or whisky'. One of the patients in the present series (Case 3) developed fever after the first occasion on which he had alcohol-induced pain. One patient in the present series had never taken alcohol before her biopsy was done; when tested afterwards with brandy she developed severe pain. If the histological changes are the result of alcohol-induced pain they should have been absent in her case. Her score for eosinophils was 9 (average for the positive group 7·85) and for fibrosis 6 (average 7·97). The scatter among these scores being what it is, no conclusion can be drawn from a single case. This patient is, however, the only one in the positive group with an indisputably normal white-cell count (5,600 per cu. mm.). The leucocytosis so regularly encountered in these patients may result from the pain, but further observations would be needed to establish this point. The main difficulty in the way of the hypothesis that alcohol-induced pain causes the changes in the nodes is that such changes are just as marked in nodes from alcohol-positive patients who had never felt pain in these nodes, as shown in Table IX. One of the most striking examples of dense fibrosis was in a lymph-node excised from a man

(Case 8) who did not have alcohol-induced pain until five years later. The hypothesis must therefore be made more complex, and consequently less attractive, by supposing that, in these patients, taking alcohol leads always to eosinophilic infiltration and fibrosis, but only sometimes to pain. Of the clinical features correlated with alcohol-induced pain, spontaneous pain and a leucocytosis are in keeping with the presence of an inflammatory component in the diseased nodes, and the same considerations apply to them. They cannot apply, however, to the increased prevalence of mediastinal involvement. It is inconceivable that alcohol-induced pain, whatever effect it may have on the histological appearances of the disease, should also affect its distribution. It is therefore necessary to look elsewhere for the explanation of this peculiarity, and if for this one, then possibly for the others as well.

The second possibility is that alcohol-induced pain is dependent upon the unusual histology found in the nodes, and not the cause of it. The chief evidence for this view is the occasional occurrence of the symptom in other inflammatory lesions, particularly osteomyelitis. This conception fails, as did the last, to account for the increased prevalence of early involvement of the mediastinum. If alcohol were to cause swelling of diseased nodes, then fibrosis, such as that shown in Fig. 3 (Plate 8), might render such swelling painful by restricting it mechanically. This attractively simple idea must be rejected, because some of the most fibrotic nodes in the series were from patients who had alcohol-induced pain, but not in those particular nodes. Thus some additional factor would be necessary for the production of pain.

There remains the third of the above possibilities, namely that Hodgkin's disease includes a separate entity, which has the features listed on page 58, and in which there is a liability to alcohol-induced pain at some stage. The early appearance of mediastinal involvement in such a syndrome suggests that the disease may start in the chest. It is therefore natural to examine the present findings in relation to Thomson's (1955) hypothesis that Hodgkin's disease always starts in the chest, being a metastasizing tumour of thymic origin. There having been no specially intended radiological search, the absence of evidence of a thymic mass in these cases cannot be taken as an objection. In Case 1 of Godden, Clagett, and Andersen (1956) the patient was subjected to a thoracotomy, at which was found 'an infiltrating mass, that apparently arose from the thymus, and involved the pericardium and pleura anteriorly'. The histological appearance was that of a granulomatous type of Hodgkin's disease. James, Harley, Horton, and Storring (1957) reported (Case 1) a patient with alcohol-induced pain who, at thoracotomy, was found to have a tumour arising in the anterior mediastinum and infiltrating the pericardium, lungs, and pulmonary artery. Histologically this tumour was a carcinoma, probably of thymic origin.

A further association lends support to the concept here advanced. The excess of men usually seen in Hodgkin's disease is found neither among those patients who have alcohol-induced pain (Tweeddale, Whelan, and Browning, 1958) nor among those who show early evidence of a thymic mass (Thomson, 1955). Thomson recorded the sex incidence in a series of 112 patients who had a mass

in the region of the thymus at the time of presentation or within a year of diagnosis. The figure is given in Table XI, together with the sex incidence in 1,506 cases of Hodgkin's disease given by Wallhauser (1933) and by Baker and Mann (1939), and also in 59 cases of Hodgkin's disease with alcohol-induced pain (50 cases from those authors listed in Table I who gave the sex of their patients, and nine fresh cases from the present series). The percentage of men is greater in the large series of Hodgkin's disease than in the series with alcohol-induced pain, and the difference is significant ($\chi^2 = 7{\cdot}9$; $P<0{\cdot}01$). This difference is probably greater than appears from these figures, for two reasons.

TABLE XI

Sex Incidence among Patients with Alcohol-induced Pain and Patients with an Early Thymic Tumour

	Number of patients	*Percentage of men*
Unclassified Hodgkin's disease .	1,506	69·8
Hodgkin's disease with alcohol-induced pain	59	52·5
Hodgkin's disease with an early thymic mass . . .	112	45·6

First, the large series of Hodgkin's disease may be presumed to have contained some patients who had alcohol-induced pain. If the incidence of such patients was 17·1 per cent. (Table II), of whom 52·5 per cent. were men, the series may be calculated to have contained 1,249 patients who did not have alcohol-induced pain, among whom the percentage of men was 73·4. Secondly, the alcohol-positive patients in Table XI represent all those published cases in which the sex is given; relatively more women being abstainers, there is probably a bias in favour of men. A more reliable estimate could be obtained from the cases of alcohol-induced pain which were found during a systematic search for the symptom; in only 27 of the 35 so found was the sex given; there were 14 men and 13 women. Table XI also shows that of Thomson's patients with early evidence of a thymic mass 45·6 per cent. were men. Taken together, the data in the Table suggest that an approximately equal sex incidence should be added to the list of features of the syndrome here defined; this contrasts with an almost 3:1 preponderance of men in Hodgkin's disease without alcohol-induced pain.

Thomson's cases with an early thymic mass were also distinguished from the others in having a rather better prognosis. The mean period of survival from the time of diagnosis was 50 months in the former and 37 months in the latter. No comparable figures are available for the present series, but the lower scores for reticulum-cell mitoses in the alcohol-positive patients suggest that the disease is relatively less malignant in them.

In putting forward the suggestion that patients with Hodgkin's disease who have alcohol-induced pain are suffering from a separate disease which starts in

the chest and has the other atypical features listed, the author would prefer, on present evidence, to leave open the question of whether the thymus is the origin of the disease in these patients.

I am much indebted to Dr. A. G. Heppleston, Dr. H. J. Whiteley, and Dr. W. Jones Williams, of the Department of Pathology, Welsh National School of Medicine, for carrying out the histological comparison, and to the many physicians and pathologists who sent me patients, case notes, or sections; also to Mr. P. D. Oldham for help with statistical analysis; to Mr. R. Marshall for the photograph, and to Professor Harold Scarborough and Professor J. Gough for helpful advice.

APPENDIX

The following are the histories of the eight patients with Hodgkin's disease and alcohol-induced pain who have not been, or are not to be, reported elsewhere.

Case 1. A man aged 26 complained in August 1955 of pain in the left side of the chest, which had been present for three weeks. A lump had been present on the left side of the neck six months previously, and had disappeared after a month. Another lump had appeared in the right side of the neck five days previously. His general health had been good.

On examination there were enlarged lymph-nodes in the right supraclavicular fossa, both axillae, and the left groin. The liver edge was felt three finger-breadths below the costal margin; the spleen was not felt. The temperature was 98·6° F, the pulse-rate 100, and the erythrocyte sedimentation rate 87 mm. in one hour. The total white-cell count was 11,800 per cu. mm. A radiograph of the chest showed enlarged right paratracheal and left hilar nodes. A node removed from the right supraclavicular fossa showed Hodgkin's disease. He was given chemotherapy, and later radiotherapy also. In January 1957 he complained of pain in the back, and in December 1957 of pain in the right iliac fossa. In March 1958 it was noted that the abdominal pain was made worse by any form of alcohol. This aggravation persisted until September 1958, when it disappeared after further treatment.

Case 2. A married woman aged 39 complained in July 1957 of feeling unwell, and of pain in the left lower chest and abdomen. She first had enlarged lymph-nodes, in the neck, in 1947, when a biopsy (specimen not available) had shown Hodgkin's disease.

On examination in 1957 there was a node in the left axilla, and the liver and spleen were enlarged. The temperature was 98·4° F, the pulse-rate 90, the haemoglobin 70 per cent., and the total white-cell count 10,300 per cu. mm. There was enlargement of the left hilar nodes; the left diaphragm was raised, and there was some pleural reaction at the left base. Biopsy of an axillary node showed Hodgkin's disease, and she was treated with nitrogen mustard. In May 1958 she began to have pain in the right upper chest, passing to the inner side of the left arm, and occurring after alcohol in any form.

Case 3. A man aged 28 complained in January 1958 of a tender swelling in the right groin, present for 18 months. For a month it had been aching sufficiently to keep him awake at night. He felt ill, had become thin, had sweated, and had had rigors.

On examination two enlarged and slightly tender lymph-nodes were found in the right groin. There were no other enlarged nodes, and the liver and spleen were not felt. His temperature was 99·2° F, and pulse-rate 100. The total white-cell count was 11,300 per cu. mm., and the erythrocyte sedimentation rate 28 mm. in one hour. A chest radiograph was normal. Biopsy of a node from the groin showed Hodgkin's disease. He was given radiotherapy. In July 1958 he began to have pain in the left flank, going into the back. The following month he drank some beer, and afterwards developed a fever; thereafter the pain in the left side became worse after he took alcohol. After treatment with nitrogen mustard the pain was only slight.

Case 4. A woman aged 34 complained in January 1952 of a painful lump in the right axilla. She had not felt ill. No other nodes were found on examination. The temperature was 99° F, and the white-cell count 11,200 per cu. mm. A chest radiograph showed enlarged nodes at the left hilum. In 1955 she noticed low backache after drinking alcohol, and at the same time she began to experience itching. The pain was relieved after treatment with nitrogen mustard, and did not recur until her death in February 1957.

Case 5. A man aged 31 complained in February 1958 of low backache, for which he took 'disprin'. For about 18 months he had lost his usual energy. In March some beer, which he took before going to an opera, made the pain very much worse, and pain persisted throughout the first act. During an interval he took some sherry, which again caused very severe pain. Two months later he collapsed with pain at a wedding at which he had taken sherry, and on another occasion he had pain after taking beer. In July 1958 he had a sore throat, and then noticed swellings in the neck which were painful, especially in the mornings.

On examination there were tender lymph-nodes in the neck; the skin over some of them was inflamed. The temperature was 98·8° F, the white-cell count 10,000 per cu. mm., and the erythrocyte sedimentation rate 5 mm. in one hour. A radiograph of the chest showed bilateral pulmonary infiltration and enlarged right paratracheal nodes. A radiograph of the lumbar spine showed sclerosis of the body of the fourth lumbar vertebra. After he had received radiotherapy and chemotherapy he was much improved, and had no pain in the back.

Case 6. A man aged 22 complained in April 1957 of pain in the right shoulder, present for three weeks. He had felt ill, and his appetite had been poor. He had lost 7 lb. in weight, and had been troubled by attacks of shivering and by cough.

On examination there were enlarged nodes in the neck and in both axillae. There was doubt as to whether the liver and spleen were palpable. The temperature was 100·2° F, and the pulse-rate 96. The haemoglobin was 70 per cent., the white-cell count 11,400 per cu. mm., and the erythrocyte sedimentation rate 83 mm. in one hour. A chest radiograph showed enlargement of the hilar and paratracheal nodes. Biopsy of a node from the neck showed Hodgkin's disease. He received radiotherapy. In December 1957 he complained of pain in the back, made worse by taking alcohol.

Case 7. A woman aged 44 complained in January 1957 of swellings in the neck, present for two years: they varied in size, sometimes being as big as marbles. For a year she had had cough with sputum, tightness in the chest, and shortness of breath. She had felt tired, and her appetite had been poor. For two months the nodes had been enlarging, but they had not been painful. For two weeks she had had an irritating rash. Previously an abstainer, she had started to take brandy when her illness began; immediately after doing so she felt severe pain in the right upper chest and in the left side of the neck. She had also had the pain after beer, after whisky, and after medicine given by her doctor.

On examination there were slightly tender nodes in the neck, axillae, and right groin. There was dullness and bronchial breathing in the right upper chest; the liver and spleen were not palpable. The temperature was 99·8° F, and the pulse-rate 115. The haemoglobin was 68 per cent., the white-cell count 38,700 per cu. mm., and the erythrocyte sedimentation rate 17 mm. in one hour. A radiograph of the chest showed a large opacity occupying the right upper zone. Biopsy of the skin showed heavy cellular infiltration of the dermis, with many eosinophils and some reticulum cells. Biopsy of a lymph-node showed Hodgkin's disease (Plate 8, Fig. 3). Administration of 50 ml. of alcohol as a 20 per cent. solution by gastric tube did not cause any pain. She was treated with nitrogen mustard.

Case 8. A man aged 25, a regular and heavy drinker of beer, noticed a painless swelling in the right axilla in December 1951. At this time taking alcohol caused him no distress. The lump was removed, and section of it was thought to show an unusual inflammatory process rather than a neoplasm. Another swelling appeared in the neck in January 1952; the overlying skin was reddened. Because of the uncertainty in the diagnosis this lump was also removed; section of it showed Hodgkin's disease. At this time the patient felt quite well in himself. The temperature was 100·2° F, the pulse-rate 104, and the total white-cell count 16,000 per cu. mm. A radiograph of the chest showed uncertain enlargement of the upper mediastinal shadow. He was given radiotherapy and nitrogen mustard.

In March 1953 a mass appeared in the left iliac fossa, and in May the liver became palpable; both regressed on treatment with nitrogen mustard. In October 1953 masses appeared in both iliac fossae and in the left side of the neck. In May 1954 there were masses in the right iliac fossa and in both groins. In September 1954 there were painful lumps in the right side of the neck. In August 1955 a large mass appeared on the right wall of the chest. All these recurrences were treated severally with radiation or with nitrogen mustard. He continued to drink heavily, and had no pain after drinking.

In September 1956 he was found to be anaemic, the haemoglobin being 48 per cent.; there was a mass in the left side of the abdomen; he was given nitrogen mustard. At the end of 1956 he noticed pain in the right flank and right side of the abdomen; the pain was slight, and was relieved by aspirin. It was, however, greatly worsened by alcohol: five minutes after drinking the pain would become very severe and remain so for 15 or 20 minutes, when it would stop fairly suddenly. It became so bad that he eventually stopped taking alcohol. By March 1957 he had lost three stone in weight, and was deeply pigmented. A mass was palpable in the central abdomen. Intravenous administration of 25 ml. of 20 per cent. alcohol caused the right-sided abdominal pain on the five occasions on which it was tried. Soon after this he developed obstructive jaundice. All his symptoms remitted after nitrogen mustard, except that he still developed slight pain after drinking beer. In April 1958 he again became jaun-

diced and wasted, and the spleen became palpable for the first time; nitrogen mustard again caused a remission. When last seen, in January 1959, he was free of jaundice, but had an abdominal mass. A little wine, which he took at Christmas, had caused right-sided pain.

Summary

The literature relating to alcohol-induced pain is briefly reviewed.

Thirteen patients with Hodgkin's disease who had had alcohol-induced pain have been compared with 20 who had not.

A histological comparison has been made independently by three observers who were ignorant of the histories of the individual patients. All three found fewer reticulum-cell mitoses, more eosinophils, and more fibrosis in sections from the patients who had had alcohol-induced pain.

The patients with alcohol-induced pain had much more often, at the time of biopsy, spontaneous pain, mediastinal involvement, and a leucocytosis.

After discussion of possible causes of the pathological and clinical contrasts found, it is suggested that Hodgkin's disease with alcohol-induced pain is a separate entity. The sex incidence of this condition does not favour men, in contrast with Hodgkin's disease as a whole.

ADDENDUM

Since this paper was accepted for publication Healy (1959) has reported a patient suffering from carcinoma of the cervix uteri who had alcohol-induced pain. Biopsy showed a squamous carcinoma which was infiltrated with eosinophils.

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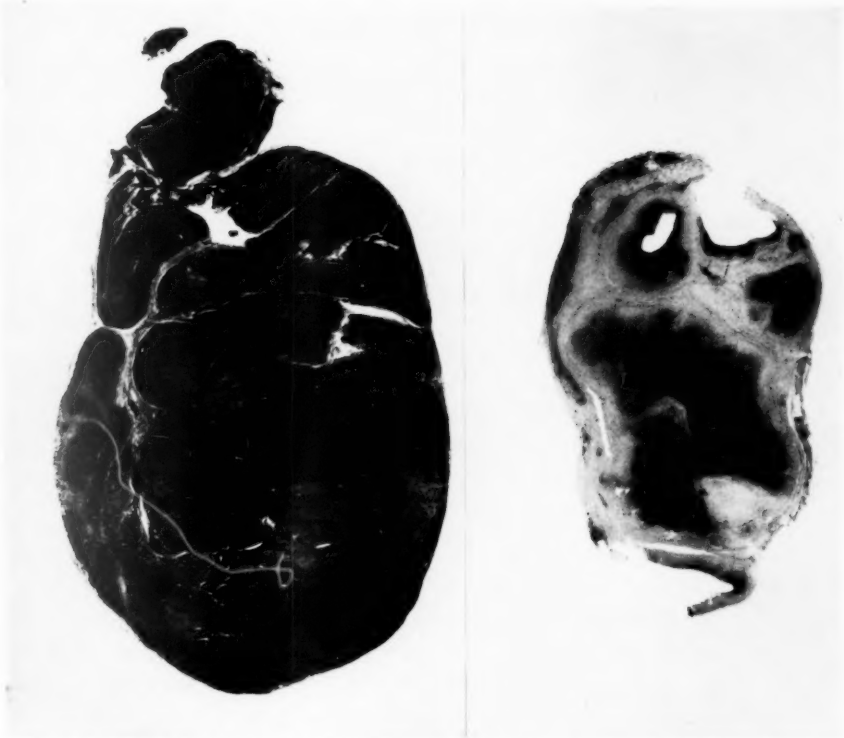

FIG. 3. Sections from a patient without (left) and another with (right) alcohol-induced pain. The latter shows conspicuous fibrosis of which the former is free ($\times 4\frac{1}{2}$)

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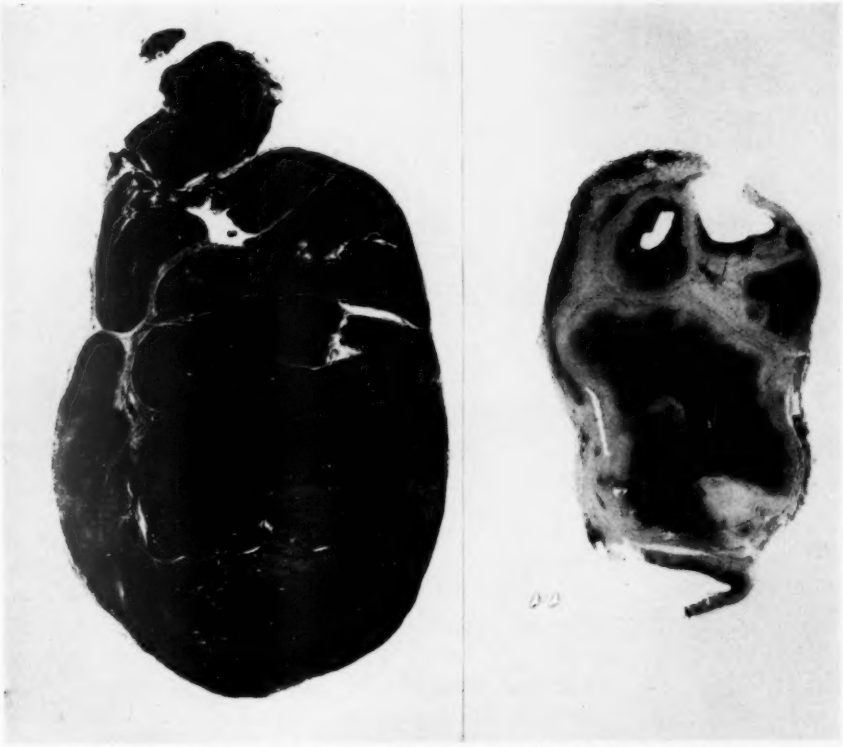

FIG. 3. Sections from a patient without (left) and another with (right) alcohol-induced pain. The latter shows conspicuous fibrosis of which the former is free ($\times 4\frac{1}{2}$)

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THE SURGICAL TREATMENT OF INTERNAL CAROTID ARTERY OCCLUSION[1]

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With Plate 9

In 1914 Hunt made a plea for more careful examination of the carotid artery pulsations in the neck in every case of cerebral vascular disease. He was struck by the fact that, although hemiplegia from occlusion of the intracranial branches of the internal carotid artery was a frequent clinical diagnosis, post-mortem examination showed that obstruction of a main artery in the neck was not an uncommon cause of this syndrome. A reason for overlooking this site of obstruction was the assumption that the circle of Willis provided a sufficient collateral circulation if the arterial block was situated below that level. The introduction of arteriography demonstrated the unexpected frequency of occlusion of the internal carotid artery in the neck (Moniz, Lima, and de l'Acerda, 1937), and since then there have been numerous papers on this subject. Hultquist (1942), in a series of 1,300 unselected autopsies, examined the internal carotid arteries in the neck, and found one of them occluded by thrombosis in 2·9 per cent. of cases. In 80 per cent. of these cases the lesion was in the region of the carotid sinus, and in the remainder it was near the origin of the ophthalmic artery. Fisher (1954) has confirmed these findings, and in a series of 45 cases of internal carotid artery thrombosis found that in every instance the lesion was due to arteriosclerosis. A number of papers have appeared recording the clinical features of this condition, including those by Johnson and Walker (1951), Fisher (1951), and Symonds (1957). There is general agreement on the variability of the symptoms and signs, and the classical history of ipsilateral blindness and contralateral hemiplegia is certainly rare. Some patients are asymptomatic, and others gravely disabled.

There have been few references to the treatment of internal carotid artery thrombosis. Anticoagulants have been tried in the belief that the common transient symptoms are the result of cerebral emboli (Millikan and Siekert, 1955), and also to prevent a partial carotid occlusion from becoming complete. Interruption of the sympathetic fibres in the neck has been tried, by stellate ganglion block or by direct surgery (Poppen and Baird, 1952). The recent advances in vascular surgery have greatly improved the results of operations on diseased

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arteries. The introduction of hypothermia has increased the scope of these procedures, for under such conditions the blood-supply to vital organs may be cut off for much longer periods than was previously possible. The first patient successfully operated on for a partial occlusion of an internal carotid artery was reported by Eastcott, Pickering, and Rob in 1954, and the first review of a large series was given by Rob and Wheeler in 1957. The purpose of the present paper is to assess the role of reconstructive arterial surgery in the treatment of internal carotid artery thrombosis by a detailed follow-up of a series of patients in whom this form of treatment was considered.

Patients Studied

The paper is based on the study of 40 patients admitted to St. Mary's Hospital during a period of three and a half years. All were found to have a complete or partial internal carotid artery occlusion in the neck, and all were considered for operative treatment. Their ages varied between 47 and 76 years, with an average of 58 years. Thirty-two were men, and eight were women. The left artery was the site of the lesion in 27, and the right in 12. In one patient both arteries were blocked, although the symptoms were confined to the right side of the body. Twenty-seven of these patients have already been considered in a review of the surgical treatment of internal carotid artery thrombosis (Rob and Wheeler, 1957). The onset of the illness took three main forms. (1) The patient might suffer a series of episodes, frequently recovering completely between them; they most commonly took the form of transient blindness or transient weakness of a limb, usually the arm. This type of onset will be referred to as 'stuttering', even when the patient is ultimately left with a permanent disability. (2) The illness might start suddenly as a single episode, and therefore resemble other kinds of cerebrovascular catastrophe. (3) The symptoms might gradually accrue, and mimic those of a cerebral tumour, although such a history sometimes ended with the sudden development of a more severe disability. There were 19 patients in the first group, 14 in the second, and seven in the third.

Symptoms. Impairment or loss of consciousness happened in only eight patients, in six at the start of the illness and in two several months after the onset. The commonest symptom was a weakness of one side of the body, which might be widespread or might affect only certain parts such as the face or hand, and might be transient or permanent. When it was permanent, there might be some improvement in the ensuing weeks or months, but it seemed unlikely that full recovery would occur. Some histories were of recurring transient attacks of weakness, each more severe, until the last one left a permanent disability. Table I shows the number of patients who complained of weakness of the face, arm, and leg, and it will be seen that the arm was most frequently involved. This finding supports the view that in carotid artery insufficiency it is the tissues supplied by the terminal branches of the middle cerebral artery that suffer most severely. Sensory disturbances were less frequent (Table II),

and all but one of the 15 patients who gave such a history also complained of weakness. Again it was the arm which was most commonly involved. The sensory symptoms were twice as often transient as permanent, while a history of permanent weakness predominated. Dysphasia occurred in 25 patients, in eight in the form of brief attacks only. Three patients with a persistent disorder

TABLE I

The 36 Patients with Motor Symptoms

	Symptoms transient	*Symptoms transient, becoming permanent*	*Symptoms permanent from onset*	*Total*
Face . .	6	0	3	9
Arm . .	13	3	20	36
Leg . .	11	3	18	32

TABLE II

The 15 Patients with Sensory Symptoms

(All but one of these had motor symptoms also)

	Symptoms transient	*Symptoms transient, becoming permanent*	*Symptoms permanent from onset*	*Total*
Face . .	2	0	1	3
Arm . .	9	0	5	14
Leg . .	6	0	2	8

TABLE III

The 30 Patients with Motor Signs, and 11 with Sensory Signs, at the Time of Admission to Hospital

(All the patients with sensory signs had motor signs as well)

	Motor signs	*Sensory signs*
Face . .	22	6
Arm . .	28	11
Leg . .	23	10

of speech also gave a history of previous transient dysphasia. Ten patients suffered from headaches. In only one was the history suggestive of migraine. Epileptic fits occurred in four cases. There were five examples of transient attacks of impaired vision of the eye on the side of the affected artery, and two in which the vision of this eye was permanently affected. Three patients gave a history of hemianopia. Only five patients spontaneously complained of a defect of memory, or of any other symptoms which suggested mental deterioration. Three patients gave a history of faintness, one of postural vertigo, and two of dizziness. In one case there had been ptosis on the side of the affected artery for a brief period. The length of the history varied from two days to five years. The one patient with a five years' history had complained of

migrainous headaches for several years before the onset of other symptoms, and these headaches may have been due to carotid artery insufficiency. The majority had a relatively short history. In 24 patients it was of less than six months, and in a further six of less than a year.

Signs. A bruit was heard over the eye on the side opposite to the carotid occlusion in two patients. Accurate testing for evidence of dementia was not always carried out, but nine showed undoubted impairment of intellect. In one there was a severe lack of emotional control. Disorders of speech were common, as would be expected from the frequency of left-sided lesions, 19 patients having a preponderantly expressive type of dysphasia. Two patients had a pale optic disk on the side of the arterial lesion; both had a history of over a year's duration. Only one patient showed more than slight arteriosclerotic changes in the retinal vessels. One of the patients with optic atrophy had diminished visual acuity of the affected eye, and one other patient, who had marked hypertensive changes in the retina, had defective vision on the side of the carotid lesion. There were eight examples of homonymous hemianopia, four on the left side and four on the right. One patient had an oculomotor nerve lesion, and one, during the acute stage of the illness, had difficulty in looking to the side of the hemiplegia. The former died, and at autopsy a haemorrhage was found in the region of the oculomotor nucleus. Thirty patients had an upper motor neurone weakness on one side of the body, and 11 of these had sensory abnormalities. The distribution of these findings is given in Table III. It will again be seen that the arm was more frequently involved than other parts of the body. The reflexes were in the majority of cases appropriate to the hemiplegia, but in three patients a unilateral increase of the deep reflexes was the only evidence of pyramidal tract involvement, and in six cases bilateral reflex abnormalities denoted more widespread cerebral damage than the other signs would have indicated. Observations by different examiners concerning the carotid pulses were too inconsistent to be of value. Twenty-two patients had a systolic blood-pressure of over 150, and 19 had a diastolic blood-pressure of over 90.

Special investigations. Carotid angiography was performed in 38 patients. It showed a complete block of the internal carotid artery in 19 cases (Plate 9, Fig. 1). Thirteen of these cases were left-sided, five were right-sided, and one was bilateral. In one patient there was a complete block of the left common carotid artery. A partial occlusion of the internal carotid artery was demonstrated in 18 patients (Plate 9, Fig. 2), in 12 on the left and in six on the right side. The block of the internal carotid artery, whether complete or partial, was either at its origin or within a centimetre of it. One of the two patients who had no arteriogram was found to have a complete thrombosis of the internal carotid artery, and the other a partial occlusion, at operation. Twelve patients had bilateral carotid arteriograms. One of these, as has already been mentioned, had a complete block of both internal carotid arteries. Four patients had a complete occlusion on one side and a normal artery on the other; two had a complete occlusion on one side and a partial occlusion on the other; three had

a partial occlusion on one side and a normal artery on the other; and one had a partial occlusion on both sides. One patient had a partial occlusion of one internal carotid artery in the neck, while the other artery was normal in the neck, but showed marked irregularities in the cavernous sinus. Electroencephalography was performed on 19 patients, the interval between the onset of the illness and the date of the test varying considerably. The record was normal in seven cases, and showed focal abnormalities on the appropriate side in 10, and diffuse bilateral abnormalities in two.

Surgical treatment. Thirty-two patients underwent operation, and it was found possible to remove the obstruction in 18. A partial occlusion of the artery had been demonstrated by arteriography in 14 of these 18 patients, and a complete occlusion in two. These two patients were operated on three and five days respectively after the onset of the illness, when the clot had not become firmly enough attached to the vessel wall to prevent removal. One of them died two days later, and at autopsy was found to have a myocardial infarct, a pulmonary embolus, and an embolus blocking the middle cerebral artery. The other improved slightly in a few days after operation, but has remained dysphasic and hemiplegic ever since. One patient was operated upon without previous angiography, and a partial obstruction of the internal carotid artery was found and removed. Another patient was shown by arteriography to have a complete block of the internal carotid artery on the side opposite to a hemiplegia, and a partial block on the other. The partial occlusion was removed in an effort to increase the total blood-flow to the brain. It was found impossible to re-establish a blood-flow in the remaining 14 patients; a previous arteriogram had demonstrated a complete occlusion in 13, and in the remaining patient no arteriogram had been done.

No operation was performed on four patients with complete and four with partial internal carotid occlusion, shown on arteriography. The reasons for not operating were varied. A complete bilateral internal carotid block was demonstrated arteriographically in one patient. Another showed clinical evidence of bilateral cerebral disease, with angiograms showing a complete arterial block on one side, a partial block on the other side, and a good collateral circulation. A third patient, with a complete occlusion, had a severe dysphasia and right hemiplegia, which had not improved in the previous 10 months. A fourth had no significant disability apart from an expressive dysphasia, which was steadily improving. Of the four patients with partial carotid occlusions, one was suffering from advanced renal disease, and one developed a coronary thrombosis while in the ward. In another a bilateral carotid arteriogram showed evidence of partial stenosis on both sides, as well as arteriosclerotic changes in the terminal portions of these arteries, but no clinical evidence of cerebral damage. One patient was admitted the day after she had suddenly lost consciousness and developed a left hemiplegia. Examination showed, in addition, a complete third cranial nerve palsy, which led to a diagnosis of a ruptured cerebral aneurysm. On bilateral carotid arteriography the contrast medium was seen to reach the base of the skull through a narrowed channel on the right side, while

no abnormalities were seen on the left. It was still thought that a partial carotid thrombosis might have occurred as a complication of a leaking cerebral aneurysm. The patient died three days later; autopsy showed a gross narrowing of the right internal carotid artery at its origin, due to haemorrhage into an atheromatous plaque, and complete thrombosis of the terminal portions of the internal carotid artery and of the middle cerebral artery on this side. The thrombosis had caused infarction of a large part of the right cerebral hemisphere, with 'secondary' haemorrhages within the brain-stem.

Surgical Technique

When the occlusion of the internal carotid artery is complete, a local or general anaesthetic is sufficient. When the occlusion is partial, hypothermia is desirable. For hypothermia we have used surface cooling, and reduced the body temperature to 29° to 30° C when it is safe to clamp the arteries for 20 to 30 minutes. The bifurcation of the common carotid artery is exposed. The carotid sheath is opened, and the common, external, and internal carotid arteries are isolated and a tape passed round each vessel. At this stage the hypoglossal nerve should be identified, and gently retracted upwards and medially. The surgeon can now assess the state of the arteries and decide upon the procedure. In patients with atherosclerotic occlusions of the internal carotid arteries he will find one of four abnormalities: a complete thrombosis extending from the carotid bifurcation into the skull; a localized plaque of atheroma, usually at the origin of the internal carotid artery, with an apparently normal artery distal to this diseased zone; occasionally, a ring-like plaque of atheroma near the origin of the internal carotid artery; or, even less frequently, a series of atheromatous plaques extending along the whole cervical course of the internal carotid artery. The treatment of each type is different.

In established complete occlusion it will be impossible to obtain a back-flow, because an organized clot will have extended as far as the first branch from the internal carotid artery inside the skull; but in some early cases it will be possible to obtain a back-flow by applying gentle suction and removing the clot. It is only in this latter type of complete thrombosis that the surgeon can perform an operation for reconstruction. If the back-flow is obtained, one should apply a bulldog clamp to the distal end of the artery and inject 5,000 units (62·5 mg.) of heparin into the lumen of this distal segment. Continuity may then be restored by the insertion of an artery or vein graft, or by the operation of thromboendarterectomy; the latter is the simplest procedure, and should be performed when possible.

A partial occlusion due to a localized atheromatous plaque is best treated by thromboendarterectomy under hypothermia. After exposure of the vessels every instrument should be carefully checked before the internal carotid artery is clamped, so that the period of occlusion may be as short as possible. First the external, then the common, and finally the internal carotid artery is clamped. Five thousand units (62·5 mg.) of heparin are injected into the

internal carotid artery distal to the clamp. A longitudinal incision, about 2 cm. long, is now made in the wall of the proximal part of the internal carotid artery. A plane of cleavage is apparent in the media; with a blunt dissector this plane is opened, so that the surgeon removes the plaque of atheroma, the intima, the internal elastic lamina, and the inner half of the media. This portion of the arterial wall should be removed from the whole length of the vessel opened by the incision. The surgeon leaves in place the adventitia, the external elastic lamina, and the outer part of the media. The lumen of the vessel is now carefully washed with saline to remove all debris, and the incision in the vessel wall closed with a continuous suture of ooooo silk. Ten ml. of 1 per cent. protamine sulphate are now given to counteract the heparin. The next step is to remove the clamps from the internal, external, and common carotid arteries. Light pressure with a swab controls the initial oozing, and the operation field should be dry in less than five minutes. The surgeon should try to keep the period of carotid occlusion to a maximum of 20 minutes. No anticoagulants are given in the immediate post-operative period.

A partial occlusion due to a ring-like band of atheroma is a rare lesion, and is best treated by a resection of the involved segment and an end-to-end anastomosis between the internal and common carotid arteries. The early stages of the operation are similar to those already described, with the difference that the whole length of the cervical portion of the internal carotid artery should be mobilized to get sufficient length for a direct end-to-end anastomosis. About 1 cm. of the internal carotid artery is now removed, and anastomosis of the two ends secured with ooooo silk. In some cases it is necessary to divide the external carotid artery in order to get sufficient mobility to perform the end-to-end anastomosis. The fourth type of lesion, with multiple plaques of atheroma, should usually be treated conservatively. If, however, surgery is thought to be advisable, only a blood-vessel graft can restore a normal lumen to an internal carotid artery of this type.

If hypothermia has been used, the patient must be carefully observed until the body temperature has returned to normal. This means a half-hourly check on the pulse-rate and blood-pressure, and a continuous record of the temperature, preferably with an indwelling rectal thermometer. It is important to maintain the blood-pressure at its pre-operative level. A fall of blood-pressure may be due to too rapid re-warming, in which case a reduction in the re-warming rate is usually sufficient to raise it. In other patients a blood transfusion will be needed. The patients should get up for bed-making within 24 hours of the operation, and then for increasing periods each day. They can leave hospital after one week, unless prevented by the neurological abnormality. When long-term anticoagulants are used, they may be started 48 hours after the operation. Our preliminary conclusions are that the best results follow a direct end-to-end anastomosis, but for technical reasons this is seldom possible. The next best procedure is a thromboendarterectomy; the insertion of an arterial transplant or venous graft is the least satisfactory. We prefer a thromboendarterectomy for two main reasons. First, the results are good, and second, the procedure is

not as complicated as a blood-vessel grafting operation. We believe that a thromboendarterectomy works in this situation because the plaque of atheroma is well localized, and above all because the distal artery has a surprisingly normal wall. This means that the outflow is good, and recurrent thrombosis uncommon.

Follow-up Examination

In October 1957 a reappraisal was made of all the patients in this series. Twenty-eight were examined by two of the authors personally, three were reported on by other doctors, and nine had died. The follow-up interval varied between one month and three and a half years. In eight cases the period was less than six months, in 12 between six months and one year, and in eight between one and two years. Three were seen again after longer intervals. Eleven patients were deemed to have improved, and it was thought that the condition of 20 had not significantly altered. It was also noted whether they had been able to return to their previous employment or to work of any kind. If the disability was sufficiently severe to prevent this, inquiry was made as to whether the patients were able to care for themselves or were complete invalids.

Improvement. Six of the 11 patients who had improved were asymptomatic, but all but one of these six had had no abnormal signs before operation except for minor reflex changes; this patient has been reported before (Edwards and Rob, 1956). Four of them had given a history of recurrent episodes, usually of muscle weakness, and had had a partial internal carotid occlusion removed. The illness of another, who had a partial occlusion successfully removed, had started suddenly. The sixth patient, with attacks of left-sided blindness and right-sided weakness, had been found to have a complete left internal carotid occlusion, and it had not been possible to re-establish the blood-flow. When this patient left hospital he had no symptoms, and he soon resumed his former work. There was no return of his previous symptoms, and he remained in good health for the next five months. He then developed a severe left hemiplegia and, although no arteriogram was performed, it was considered possible that this was due to a right internal carotid thrombosis. As there had been a complete cure of his initial symptoms, it was concluded that, as far as the left internal carotid thrombosis was concerned, the natural processes of recovery had resulted in improvement, and the patient was classified accordingly. All these six patients had returned to their previous employment.

Three of the other five patients who were considered to have improved still had symptoms and signs, but insufficient to prevent them returning to work. One of these was a housewife who is still at work, and her case has been reported before (Eastcott, Pickering, and Rob, 1954). She had a 'stuttering' type of onset, and a partial carotid occlusion was removed. The other two patients had a complete block of one internal carotid artery, and one underwent operation, with no restoration of the blood-flow. Two patients had improved, but were still so disabled that, although they could care for themselves, they had

been unable to work. They each had a complete block of one internal carotid artery and, although operation was done, no back-flow of blood could be obtained.

No change. Twenty patients showed no significant change. In seven of them a partial carotid occlusion had been removed. A further seven underwent operation, but nothing could be done to restore the blood-flow. Six had no operation. All but one of those seven who were successfully operated upon had a partial obstruction of the artery. The one with a complete occlusion has already been referred to (page 71), the significant point in the history being the very recent occurrence of the thrombosis five days before operation. Twelve of the remaining 13 patients had a complete internal carotid artery occlusion. One of these has been considered as an instance of complete occlusion in which no operation was performed, for this artery was blocked on the side opposite to a hemiplegia. Since, however, the opposite internal carotid artery was partially occluded, it was explored, and the obstruction successfully removed. Another had a complete occlusion of both internal carotid arteries. His condition had deteriorated within a few hours of arteriography and, although a marked improvement had followed, this was not complete. This episode was considered to be a complication of the arteriography, and not to be related either to treatment or to the natural course of the disease; it was therefore not taken into account when assessing the patient's present state, and he was classified among those whose condition had not materially altered. The last patient in this group had a partial occlusion of both internal carotid arteries with no clinical evidence of cerebral damage, and was not operated on for reasons that have already been given. This patient, and one other with a complete carotid artery occlusion and no neurological abnormalities, had returned to their previous employment. Three of the patients in whom a satisfactory blood-flow was restored at operation were able to care for themselves, but could not work, and four were complete invalids. Seven of the patients with a complete and unrelieved internal carotid artery occlusion could look after their personal needs, and four were complete invalids.

Mortality. Nine patients had died. In only two cases did death occur before discharge from hospital. The first was that of a man aged 71 who, after a series of episodes, had suddenly become dysphasic and hemiplegic. An arteriogram had shown a complete block of the left internal carotid artery, and at operation this artery was found to be occluded by thrombus from the bifurcation into the skull, no back-flow being obtained in spite of passing a catheter into the intracranial portion of the artery. He died three days later. Autopsy showed a pulmonary embolus arising from thrombosis in the popliteal veins. The second patient was operated on three days after a left hemiplegia, which arteriography had shown to be due to a complete internal carotid artery occlusion. Blood-flow was re-established, but two days later he died. Autopsy showed an extensive myocardial infarction and a pulmonary embolus, as well as an embolus blocking the right middle cerebral artery, with infarction of a large part of the hemisphere. These two deaths were not the result of complications peculiar to the

operation under discussion. Three patients died of cerebral haemorrhage. All had been found to have partial occlusions of an internal carotid artery, and all had had the obstruction successfully removed. The first had suddenly developed a left hemiplegia, from which she never fully recovered, the operation causing little change in her condition. Anticoagulant therapy was started a few days after operation, and subsequently she had to be admitted to hospital on two occasions because of spontaneous bruising and haematuria. She was still having anticoagulant drugs when she died seven months later. Post-mortem examination showed that the internal carotid artery had retained its normal calibre (Plate 9, Fig. 3). There was a massive cerebral haemorrhage on the right side, almost certainly due to rupture of one of the perforating arteries at the base of the brain. The ventricles were full of blood, and there were 'secondary' haemorrhages within the brain-stem. The right cerebral hemisphere also showed a circumscribed area of old infarction, no doubt the cause of the patient's original symptoms. The second of these patients had also developed a sudden hemiplegia, and at operation the appearance of the left internal carotid artery suggested that a small piece of thrombus had become detached to form an embolus. There was no change in his condition after operation, and he was discharged taking anticoagulant drugs. Eighteen days later he was admitted unconscious, and died; post-mortem examination revealed a haemorrhage of the right internal capsule. The carotid arteries were patent, and the operation scar was healing normally. This patient had stopped taking anticoagulants three days before his death. The third patient, known to be suffering from neurosyphilis, had a series of attacks of weakness of the left side of the body. After operation there were no further symptoms, but two months later he was readmitted with evidence of a posterior cerebral artery thrombosis. During this interval anticoagulant therapy had been given, and the prothrombin time was significantly increased at his second admission. On the evening of the second day in hospital he died. Permission for post-mortem examination was refused, but it was presumed that death had been due either to an extension of the cerebral thrombosis or to a cerebral haemorrhage. The fact that these three patients had been receiving anticoagulant drugs must be considered as possibly relevant.

One patient had died of coronary thrombosis over 18 months after operation. A complete internal carotid artery thrombosis had been confirmed at operation, and it had not been possible to re-establish blood-flow. There had been no change in his condition until another cerebrovascular accident, a year after operation, caused further deterioration. Three patients who died before the time of the follow-up had not undergone operation. One, as has already been mentioned, died shortly after admission to hospital from a massive cerebral infarction. The second died of renal disease, and the third of congestive heart failure.

Factors in prognosis. It may be of value to relate the follow-up findings to other features, such as the mode of onset of the illness and the re-establishment of blood-flow at operation. It must be stressed that the classification of a

patient as 'improved' bears no relationship to the degree of residual disability, and therefore it is necessary to divide such patients into three classes: those who are asymptomatic; those who are slightly disabled; and those who are still severely incapacitated.

TABLE IV

Relation between the Mode of Onset, the Degree of Carotid Occlusion, the Mechanical Success of the Operation, and the Clinical Assessment at Follow-up Examination

'Stuttering' onset: 19 patients

	Partial occlusion: 11 patients		*Complete occlusion: 8 patients*	
Blood-flow restored in internal carotid artery at operation	Improved and asymptomatic	4	..	
	Improved but slightly disabled	1		
	No change	2		
	Dead (died 2 months after operation from cerebral haemorrhage)	1		
No restoration of blood-flow in internal carotid artery	No change	1	Improved and asymptomatic	1
	Dead (one died from renal failure 2 months after discharge; one died from coronary thrombosis 4½ months after discharge)	2	Improved but slightly disabled	1
			No change	4
			Dead (one died* 3 days after operation from pulmonary embolism; one died 1 year and 8 months after operation from coronary thrombosis)	2

Sudden onset: 15 patients

	Partial occlusion: 6 patients		*Complete occlusion: 9 patients*	
Blood-flow restored in internal carotid artery at operation	Improved and asymptomatic	1	No change	1
	No change	2	Dead (died* 2 days after operation from myocardial infarction and pulmonary embolism)	1
	Dead (one died 4 weeks after operation from cerebral haemorrhage; one died 7 months after operation from cerebral haemorrhage)	2		
No restoration of blood-flow in internal carotid artery	Dead (died 3 days after admission from blockage of terminal portion of internal carotid artery and middle cerebral artery causing extensive cerebral infarction)	1	Improved but slightly disabled	1
			Improved but severely incapacitated	1
			No change	5

Gradual onset: 6 patients

	Partial occlusion: 2 patients		*Complete occlusion: 4 patients*	
Blood-flow restored in internal carotid artery at operation	No change	2	..	
No restoration of blood-flow in internal carotid artery	..		Improved but severely incapacitated	1
			No change	3

* The only two cases in which death was related to operative treatment.

The patients can be divided into three groups according to the mode of onset of their illness: 'stuttering', sudden, and gradual. In Table IV the type of onset is correlated with the degree of arterial obstruction and the mechanical success of the operation. It will be seen that the factors which give the most favourable prognosis are a 'stuttering' type of onset, a partial arterial stenosis, and the establishment of a satisfactory back-flow of blood at operation. These patients, of course, are the ones most likely to be free of permanent disability prior to operation. It might have been thought that those patients whose illness started suddenly, without previous transient symptoms, and in whom arteriography showed a partial carotid occlusion, would have an equally favourable prognosis. The fact that this is not so may be related to the suggestion that the blood-supply to a part of the brain in these patients is completely cut off rather than

impaired. This might be due to an embolus arising from the site of the partial carotid occlusion and lodging in a distal branch of the arterial system, or to a thrombosis occurring in a similar vessel owing to the slowing of the circulation. Such an obstruction might not be shown on arteriography. There is evidence for this theory in the operative and post-mortem findings in the two patients in this group who died. In the first of them the appearance of the carotid artery at operation suggested that a small piece of thrombus had recently become detached. In the second the circumscribed area of infarction found at autopsy would favour an adjacent embolic or thrombotic lesion rather than anoxia from a failing collateral circulation.

TABLE V

The Correlation Between the Patients' Capacity for Work and Various Clinical Features

	Type of onset			*Carotid occlusion*		*Results of treatment*		*Clinical assessment at follow-up examination*			
Working capacity	*'Stuttering'*	*Sudden*	*Gradual*	*Partial*	*Complete*	*Carotid obstruction removed*	*No re-establishment of blood-flow*	*Improved and asymptomatic*	*Improved but slightly disabled*	*Improved but severely incapacitated*	*No change*
Working full-time (11 patients)	9	2	0	7	4	6	5	6	3	0	2
Able to care for self (12 patients)	4	5	3	3	9	3	9	0	0	2	10
Complete invalid (8 patients)	1	4	3	2	6	4	4	0	0	0	8

A history of a gradual onset of symptoms would suggest a progressive cerebral anoxia, due to widespread vascular abnormalities affecting either the small intracranial arteries or most, if not all, of the main vessels in the neck. In either case there would be a serious interference with the formation of an adequate collateral circulation. If this were so it would be unlikely that improvement would come from surgery. The follow-up findings in the few relevant patients in this series would support this view.

In 17 patients it was possible to re-establish the blood-flow, and these included five of the six patients who were improved and asymptomatic. Arteriography had shown a partial carotid occlusion in 15. The two patients with complete occlusions were operated on within a few days of the onset of symptoms. There was no evidence that either was helped by operation. It is likely that, in order to cause any reversal of the neuronal damage, the blood-flow would have to be re-established within such a short space of time that only an emergency operation would be effective. Nevertheless, the slighter the neurological disability the stronger the argument for operation in this group of patients, for, even if the reconstitution of the artery had no effect on the patient's present symptoms, the resultant increase in the total cerebral blood-flow might influence the long-term prognosis.

On reviewing these patients from the point of view of their ability to work, it was found that 11 had returned to their previous employment, 12 were able to care for themselves, and eight were complete invalids. Table V shows the correlation between the patients' capacity to work and various clinical features. It confirms the good prognosis in patients whose illness has a 'stuttering' type of onset, and in whom the arteriogram shows a partial internal carotid artery occlusion. The relatively poor prognosis in patients with a gradual onset of symptoms supports the supposition that widespread arterial disease is prominent in this group.

Discussion

The cause of the arterial occlusion in all our patients was atheroma. The site of narrowing was at, or just distal to, the origin of the internal carotid artery. Pathological studies have shown that atheromatous narrowing also commonly occurs near the origin of the ophthalmic artery. Hutchinson and Yates (1957) have emphasized the lack of correlation between the degree of atheroma of the intracranial arteries and that found in their parent trunks in the neck. The fact that the large arteries in the neck may be severely involved, while their terminal branches frequently are not, makes the attempt to re-establish a normal blood-flow of great importance. Other diseases causing narrowing of these arteries are rare, and together are not more than a small fraction of the whole. Thrombo-angiitis obliterans has been considered as an important cause, notably by Krayenbuhl (1947), Paillas and Bonnal (1954), and Lindenberg and Spatz (1939), but no example occurred in our series. Internal carotid artery thrombosis has been noted in some of these cases, but only Fisher (1957) has considered this to be of fundamental importance. He suggested that the findings described in the small cerebral vessels are produced by 'stagnation thrombosis' due to slowing of the circulation from the occlusion of a major artery, and that cerebral Buerger's disease may not exist as a clinical entity. Examples of internal carotid artery thrombosis secondary to trauma over the neck or near the tonsillar fossa, although rare, are of considerable interest to this subject (Cairns, 1942; Schneider and Lemmen, 1952). As Fairburn (1957) pointed out, these thromboses seem less benign than one might suppose from comparison with elective ligature of the carotid artery. The cerebral effects may be disastrous, and in some cases widespread clotting has been found in the intracranial arteries. Also of interest is the patient of Boldrey, Maas, and Miller (1956), who suffered two episodes of transient hemiplegia while turning his head, and in whom the internal carotid artery was found bound to, and compressed by, the transverse process of the atlas.

Of as much interest as the cause of arterial narrowing is the mechanism of blood-flow to the brain, and the effect upon it of occlusion of the contributory arteries. In this context Brain's Harveian oration (1957) is important, especially his views of the haemodynamics of the circle of Willis. We know that a complete block of an internal carotid artery may lead to no symptoms, and

occasionally the same is true of the occlusion of more than one artery to the brain. At other times, and more commonly, stenosis of one artery leads to disablement. The effect of a gradually progressive and discrete narrowing of an internal carotid artery in the neck will depend upon the efficiency of the collateral circulation to the hemisphere on the same side. This depends upon a number of factors: the developmental anatomy of the circle of Willis, its health, the size and health of other arteries normally contributing to the circle, and of the arteries that may contribute merely as a result of the disease, and finally the efficient maintenance of blood-pressure and blood-flow. If one or more of these factors are deficient, oxygenation of a part of the brain may decrease, perhaps variably, to near the danger point, and the stage is set for the occurrence of transient symptoms. Denny-Brown (1951) referred to such episodes as 'haemodynamic crises'. They are exemplified here by one patient in whom the evidence pointed to paroxysmal tachycardia as the trigger for episodes of transient blindness and hemiparesis, and by another who developed transient dysphasia and paraesthesiae when in a hot bath.

Distal thrombosis or embolus seems an unlikely cause of repeated, transient, stereotyped symptoms. Commonly such repeated episodes end in a permanent disorder of much the same pattern as the heralding attacks, and then it may be assumed that the local circulatory failure has led to irreversible damage from anoxia, or from thrombosis with infarction. Such a final picture may result from a fault in one of many links of an already weakened chain; for instance, a sudden increase of stenosis in the internal carotid artery by an added thrombus, or by a haemorrhage beneath the atheromatous plaque. Similar explanations may account for the sudden, single, and unheralded attack of hemiplegia accompanying a stenosis of the artery in the neck. An embolus arising from the narrowed artery seems another possible cause. Permanent disability may also result from an extension upward of a clot from the site of narrowing to a point where it would impede the function of the circle of Willis. Hutchinson and Yates (1956) have suggested arterial spasm as the responsible mechanism, particularly as a complication of haemorrhage into the atheromatous plaque. This naturally occurring local trauma might be likened to the well-known results of external damage to arteries in other situations which may, for much of their length, go into an intense spasm. Such a happening may also explain the malignant effects of the traumatic internal carotid artery thromboses previously mentioned.

In the majority of patients the diagnosis of internal carotid artery occlusion in the neck cannot be made clinically. The combination of unilateral blindness with contralateral motor or sensory symptoms, both of which features may be transient or permanent, is diagnostic of an occlusion of the internal carotid artery at or below the origin of the ophthalmic artery. Such a characteristic picture is not common, and occurred in only five patients of the present series. If the ocular or other symptoms occur separately, but are episodic and transient, the diagnosis may be considered. Otherwise, when the onset is sudden, the clinical picture may be precisely that of an occlusion of the internal carotid artery above the origin of the ophthalmic artery, or of one of its terminal branches. When symptoms have developed gradually, arousing the suspicion

of an intracranial expanding lesion, it is not uncommon for arteriography to demonstrate an internal carotid artery occlusion in the neck. Occasionally a complete occlusion is found at autopsy in a patient who has had no appropriate symptoms or signs.

When the condition is suspected there are two ways of making a precise diagnosis: angiography, or surgical inspection. Angiography has been criticized on account of its dangers, which are real, though mishaps are rare. One example was encountered in the present series. It must be remembered, however, that if surgical inspection is to be combined with a possible arterial operation, the preparation of the hypothermic patient is a formidable affair and not without risk. Attempts have been made to replace arteriography by refined methods of clinical examination. Palpation of the internal carotid pulse gives inconstant results, confusion being caused by the nearby external carotid artery, and by the pulsation in the common carotid artery, which is often more vigorous than normal on the proximal side of a block. Palpation in the tonsillar area has also been tried and found wanting (Gurdjian and Webster, 1953). In the absence of a conducted murmur from the heart, a systolic bruit heard over the artery is reliable evidence of a partial stenosis, but is inconstant. It has been suggested that ophthalmoscopic examination of the retinal vessels may be of diagnostic help. In cases of carotid occlusion compression of the opposite artery, or light pressure over the globe, may cause emptying of the retinal vessels (Denny-Brown, 1951). A more accurate test has been devised, using Baillart's ophthalmodynamometer (Wood and Toole, 1957; Milletti, 1950). Even if such manœuvres are reliable, they will not differentiate between a partial and a complete carotid occlusion, and the present review has shown that this information is most important when considering surgical treatment. Therefore it appears justifiable to submit every patient with suspected carotid occlusion to arteriography if surgical treatment is contemplated. When interpreting the radiographic appearances of a partial obstruction, it is important to know that the reduction in the lumen found at operation will be greater than that visualized on the X-ray film. Operation on some patients will be prevented by the presence of other diseases. In some patients with arterial degeneration advanced renal and coronary artery disease may be found. If there is a long history of neurological disability there is unlikely to be a significant response to any form of treatment. With these reservations, any patient with suspected carotid artery disease should be investigated; and the findings in our follow-up examination suggest that the patients who will benefit most from operation will be those with a 'stuttering' type of onset and a partial arterial occlusion.

A number of papers have dealt with the attempted reconstruction of the occluded internal carotid artery, but most have referred to individual cases, and no long-term follow-up has been undertaken (Gurdjian and Webster, 1953; Strully, Hurwitt, and Blankenberg, 1953; Denman, Ehni, and Duty, 1955; Lin, Javid, and Doyle, 1956; Webster, 1956; Jackson and Fromm, 1957; Welch and Eisman, 1957; Wood and Toole, 1957). It has already been mentioned that the first review of a large number of patients treated in this way was published

by Rob and Wheeler (1957), but their findings are complementary to the present paper, and will not be further referred to. In only a few of our 18 patients in whom it was possible to restore a normal blood-flow was there unequivocal evidence that the artery remained patent. This evidence, however, was uniformly favourable, whether it took the form of post-operative arteriography, inspection at a second operation, or autopsy. A post-operative arteriogram was performed in four patients, it being considered unjustifiable to do this as a routine. In one of these patients the pre-operative arteriogram showed a partial arterial occlusion. An atheromatous plaque was removed, and a further arteriogram three weeks later showed that the flow of contrast medium was normal. At follow-up examination the patient was asymptomatic, and there was no doubt of improvement. Two others were also found to have a partial occlusion, and arteriograms performed two and three weeks respectively after operation were normal. Subsequently there was no change in their condition. The fourth patient had a complete arterial occlusion, but it was possible to restore the blood-flow. Ten days later angiography showed that the artery was patent. The carotid arteries of one patient had been re-explored before the second arteriogram because of bleeding from the wound. The presence of pulsations in the artery was confirmed. Another patient underwent a second operation because of a temporary worsening of the neurological state. A partial obstruction had been removed from the artery, and on the second inspection it was pulsating normally. This patient died from a cerebral haemorrhage seven months later, and the normal appearance of the affected artery at autopsy (Plate 9, Fig. 3) has already been mentioned. Two patients died after a satisfactory blood-flow had been restored in the diseased artery. The first died from a cerebral haemorrhage a month after operation, and examination of the artery confirmed its patency. The second died two days after operation from myocardial infarction and pulmonary embolism and, although there was occlusion of the middle cerebral artery, the previously occluded internal carotid artery was patent.

There was no evidence that anticoagulant therapy played any beneficial part in the course of the illness. It is possible that such treatment carries a risk. Two patients died of cerebrovascular catastrophes while receiving anticoagulant drugs, and one within three days of stopping them. Even if such therapy had little effect on the lesion at the carotid bifurcation, it might help to prevent the 'stagnation thromboses' that Fisher (1957) has suggested may occur in the small terminal vessels of the carotid tree. Carter (1957) found that anticoagulant therapy influences favourably the prognosis of cerebral embolism, and the work of Wright, Kubic, and Hayden (1953) suggests that the recanalization of arteries occluded by thrombi is significantly affected by these drugs. They maintained that anticoagulants prevent the continual deposition of fresh fibrin on the surface of the thrombus, and that they may also depress the growth and dividing power of the fibroblasts.

Since the number of patients reviewed is small, and the natural history of the disease is variable, it would be unwise to draw rigid conclusions from the present study. It seems, however, that the patients most likely to benefit from

operation are those with a partial obstruction of the artery whose history is of a 'stuttering' onset of symptoms; and the reason may be that the diagnosis is made before severe and permanent neurological disability has developed. The worst results, in patients with partial arterial block, are in those with a gradual onset of symptoms. The explanation may be that the gradually accruing symptoms, and possibly the single permanent episode, are associated with structural lesions other than the mere arterial narrowing; the theoretical possibilities are many, and include diffuse arterial inefficiency, spreading thrombosis, emboli, and failure of arterial pressure. The operative results with complete arterial blockage are clearly not so good; nor is the prognosis of the natural history. In the majority of such cases the surgeon cannot achieve his mechanical object, to re-establish blood-flow.

The operation should be thought of as primarily prophylactic, to prevent transient symptoms from becoming permanent and to prevent already permanent symptoms from worsening. Whether or not the operation can be curative of established symptoms is still in doubt. The ideal patient is an otherwise healthy person who is suffering from transient and completely reversible symptoms. As a rule he should have a common carotid angiogram, and be operated upon under hypothermia if a partial block is shown. The presence of a systolic arterial bruit over the supposed block might allow the omission of the angiogram. Further experience of such prophylactic surgery may lead to more frequent investigation of the arterial quartet that supplies the brain directly. Then perhaps evanescent symptoms, or the less disabling permanent ones, suggestive of anoxia of the brain-stem, cerebellum, or cerebrum, may lead to surgical repair of one or more of these arteries. In other words, the emphasis may come to be on providing more blood to the circle of Willis for distribution to the brain as a whole, so as to remedy the ischaemia in any part. Already the need is felt for bilateral carotid arteriography in cases in which the symptoms point to a block of one artery only, and thoughts are turning to the accessible reaches of the vertebral artery.

The authors wish to thank the physicians, from various hospitals, who have referred their patients for surgical treatment of carotid artery thrombosis. They also wish to thank Professor D. M. Pryce and the staff of the Department of Pathology at St. Mary's Hospital for the post-mortem reports, and Dr. D. Sutton and the staff of the Radiological Department of St. Mary's Hospital for the arteriograms performed in many of these patients.

On request the authors will supply typewritten case histories of the 40 patients included in this study. A further 30 patients have been treated since the study was completed.

Summary

1. The subject of internal carotid artery thrombosis is briefly reviewed.

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Summary

1. The subject of internal carotid artery thrombosis is briefly reviewed.

2. Forty such cases have been followed up, 32 of them after an operation for re-establishment of blood-flow.

3. The results are assessed, and an attempt made to formulate the criteria for operation.

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THE RATE OF CALCIUM TURNOVER IN BONE[1]

Measurement by a Tracer Test using Stable Strontium

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In the living body bone is a vital and dynamic tissue, whose calcium atoms are constantly being replaced by others from the surrounding fluid. The rate of this process is changed in various conditions, such as hyperparathyroidism and certain widespread diseases of bone, some of which are revealed by abnormal concentrations of calcium and phosphorus in the plasma. Since these changes of concentration probably depend on more striking abnormalities in the rate of movement of calcium into and out of the bones, measurement of this rate should be a more sensitive diagnostic procedure. While clinical and radiological examination alone may lead to the recognition of severe hyperparathyroidism or osteomalacia, these diagnoses usually require biochemical confirmation. Indeed, by such means, hyperparathyroidism is now most often found not among patients with obvious bone disease, but among those with renal calculi or other manifestations, such as vomiting (Albright, Aub, and Bauer, 1934; Cook and Keating, 1945; Albright and Reifenstein, 1948; Hellström, 1954; Bogdonoff, Woods, White, and Engel, 1956; St. Goar, 1957). The main biochemical criterion for the diagnosis of hyperparathyroidism is the presence of hypercalcaemia for which no other cause can be found; but very slight deviations in serum-calcium level may be important (Albright and Reifenstein, 1948) and, further, there are other causes of hypercalcaemia which clinically may closely simulate hyperparathyroidism (Klatskin and Gordon, 1953; McGeown and Montgomery, 1956). Similarly in early osteomalacia the serum calcium, phosphorus, and alkaline phosphatase are not always abnormal (Salvesen and Böe, 1953; Nordin and Fraser, 1956). Thus there is need of a more sensitive clinical test of calcium metabolism, both for patients showing obscure bone disease and for those in whom disordered calcium metabolism is suspected for any reason. Routine biochemical procedures measure the levels of serum calcium and the body's external losses (that is, the urinary calcium excretion and the calcium balance on different diets). But these do not indicate the body's internal movements of calcium, into and out of bone, where over 99 per cent. of the body's calcium is found. The strontium tracer test described below has been developed to enable the patient's rate of turnover of calcium in bone to be measured, and its clinical usefulness has been assessed from the results of 172 tests in 132 patients.

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Choice of a tracer. Within the body calcium follows a single metabolic pathway—a turnover through bone. The rate of this turnover should be measurable by a tracer technique, just as the turnover of iodine through the thyroid is measured with radioiodine (^{131}I). Tracer studies of calcium metabolism have been carried out in man (Lawrence, 1942; Geissberger, 1951; Bellin and Laszlo, 1953; Blau, Spencer, Swernov, and Laszlo, 1954; Staub, 1954; Bauer, Carlsson, and Lindquist, 1955*a*, 1956, 1957; Anderson, Emery, McAlister, and Osborn, 1956; Bronner, Harris, Maletskos, and Benda, 1956; Krane, Brownell, Stanbury, and Corrigan, 1956; Spencer, Brothers, Berger, Hart, and Laszlo, 1956; Bauer and Ray, 1958); but the evolution of a simple and practical test of this kind has been delayed by two factors. The available radioactive isotopes of calcium

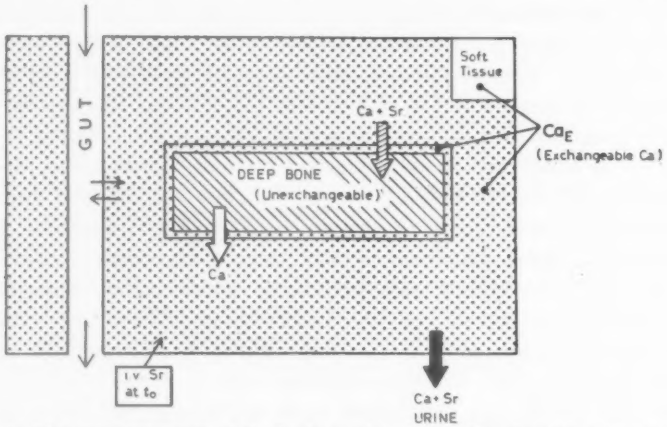


FIG. 1. The compartments of the body's calcium and the strontium tracer test.

have a dangerously long half-life (^{45}Ca has 152 days); and these tracers of calcium pass through a longer and more complex mixing process in the body than does radioactive iodine. Not all tracers, however, need to be radioactive, and analysis of the results can be relatively simple if it concerns only the main phenomenon of the tracer test, or the phase after mixing has been completed. There are many heavy elements which on entering the body are concentrated in the skeleton, and so might be calcium tracers. Two, gallium and barium, have suitably short-lived and reasonably safe radio-isotopes, but are deposited only in the bone matrix and, unlike calcium, do not enter into the bone crystals. We have studied gallium, but it did not prove a valid reflector of calcium metabolism. Strontium (Sr), however, which chemically resembles calcium (Ca) closely, appears to be deposited in the bones by the same process as calcium; it enters the bone crystals, exchanging equivalently for calcium, apparently because of its equivalent atomic radius (Neuman and Neuman, 1953). Hence, as a sensitive flame-photometric method for measuring strontium was available (MacIntyre, 1957), it seemed reasonable to anticipate that stable strontium would be a suitable tracer for measuring the bone turnover of calcium in man.

The phases of calcium metabolism in the body. (Fig. 1.) Calcium is found in the

body in bone, extracellular fluids, and soft tissues. From the body fluids calcium can enter the skeleton in two ways: by exchanging with other calcium ions on the exposed surfaces of the bone crystals, and by deposition into new bone crystals as these are formed. The first or exchange process occurs rapidly and extensively, for bone behaves rather like an ion-exchange column, whose extensive surfaces are in equilibrium with the surrounding fluid. Isotope studies, even *in vitro* with dead bone, have shown the rapidity with which this exchange can occur, for example, with ^{32}P, ^{45}Ca, and ^{90}Sr (Neuman and Neuman, 1953; Bauer, 1954*a*; Bauer and Carlsson, 1955; Bauer, Carlsson, and Lindquist, 1955*a*, 1956; Lengemann, 1957). The exchange process, however, is clearly not the sole one, for new bone is constantly being formed to keep pace with resorption. Further, autoradiographic studies have shown that injected ^{45}Ca or ^{90}Sr is initially deposited widely throughout an animal's skeleton, but later the isotope remains only in certain areas where it has become deposited in the deeper bone (Lawrence, 1942; Tutt, Kidman, Rayner, and Vaughan, 1952; Jowsey, Owen, and Vaughan, 1953; Jowsey, Rayner, Tutt, and Vaughan, 1953; Bauer, 1954*b*). Bauer and Carlsson (1955) injected both ^{32}P and ^{45}Ca into rats, and during the next five days made serial measurements of the specific activity of these isotopes in plasma and in a bone. From these measurements they computed the rate of uptake of calcium by bone (mg. of Ca per hour); for the first 24 to 48 hours the uptake was rapid, owing presumably to the summation of exchange and deposition; but thereafter mixing or exchange with the surface bone was evidently completed, and the rate remained steady, then reflecting the rate of deposition into deeper bone. These and other similar findings suggest that the surface bone is in a rapidly exchanging equilibrium with the body fluids, so that these two fractions of the body's calcium may be regarded together as comprising a pool or mass of exchangeable calcium (Fig. 1); from this pool there is a steady movement of calcium into deeper bone in the process of deposition, accretion, or bone growth. In analysing the tracer data we may therefore consider the body's calcium as existing in two main pools, the exchangeable calcium pool and the deep bone. Into the exchangeable pool calcium is received from gut absorption and from bone resorption, and from it calcium is lost by urinary and faecal excretion, as well as into deep bone by deposition. The steady transfer of a calcium tracer into deep bone may occur not only by the process of deposition of new bone, but also partly by the physical process of recrystallization, or a slow penetration by exchange into the crystals (Neuman and Neuman, 1953). But, since changes in these rates are likely to occur in parallel, and to depend on corresponding alterations in the rate of new bone formation, this possibility has no practical clinical relevance.

Analysis of the tracer data. From the foregoing one might expect that the disposal of an intravenously injected calcium tracer would occur in three phases of different rates; *phase 1*: a rapid fall of concentration in the plasma, probably of a complex pattern, mainly reflecting a mixing with the exchangeable calcium in the soft tissues and on the surface of the bone, as well as a movement of calcium in the pattern seen in the next phase; *phase 2*: a slower, simple

exponential fall in concentration, revealing the rate of removal of calcium from the exchangeable pool (into deep bone and into the body's excretions), no longer affected by the faster mixing within this pool; and *phase 3*: a gradual slowing of this fall, as skeletal resorption begins to involve deep bone now containing tracer additions.

If phase 2 can be seen separately from the others, the rate of calcium loss from the exchangeable pool should be measurable by analysis of semilogarithmic plots of this phase against time. After one or two days our semilog plots of plasma concentration and urine excretion have fallen on parallel straight lines (see Fig. 2, page 91), confirming this prediction of a separable phase 2, which should therefore reflect (1) the size of the exchangeable pool, (2) the total fractional rate of loss from this pool, and (3) the proportion of this loss due to urinary excretion. From these findings can then be derived the two main results of the tracer test: (i) Ca_E, the exchangeable calcium mass, and (ii) Ca_B, the rate of deposition of calcium in bone. The additional resorption component (phase 3) will not be measurable during the test, since at any one time only a small proportion of the skeleton undergoes resorption, and so only an insignificant amount of the deposited strontium can be resorbed within seven days. Previous analyses over long periods of time with ^{45}Ca (Anderson, Emery, McAlister, and Osborn, 1956), or radium (Norris, Speckman, and Gustafson, 1955), have shown that the rate of loss of calcium tracer from the serum after about 125 days depends on a power function of time; that is, it gives straight-line log-log plots. Such analyses are clearly concerned with phase 3 of the tracer curve.

Units used for expressing the results: The 'total plasma unit'. To express the results of this test, the 'total plasma unit' has been used, that is, the amount of calcium circulating in the patient's total plasma (estimated in litres as 5 per cent. of body weight); thus with a normal plasma calcium concentration of 10 mg. per 100 ml., one plasma unit $= \left(100 \times \frac{\text{body weight in kg.}}{20}\right)$ mg., or 5 mg. per kg. With calcium this seems preferable to the 'litre of plasma' unit, often used in tracer tests for measuring exchangeable masses by isotope dilution techniques, for some of the calcium is in solid bone; the unit also incorporates a necessary correction for body size. It is probably undesirable to express the results as mg. of calcium by multiplying by the serum calcium concentration, since we have found that Ca_E and Ca_B do not necessarily vary along with the serum level. For example, hyperparathyroidism is the only hypercalcaemic state associated with an increased turnover of calcium in bone, provided the results are expressed in total plasma units. Thus, using these units, the tracer test can have its independent diagnostic significance.

Methods

This stable strontium test has been possible because of the sensitivity and specificity of the flame spectrophotometer, developed by MacIntyre (1957), which employs a photomultiplier and an adjustable monochromator prism.

Set at 461 mμ this instrument measures strontium largely independently of calcium, which it can also measure at 423 mμ. The spectrophotometer has enabled us to measure strontium in biological fluids at a concentration of 0·01 m-equiv. per litre with an error of less than 5 per cent.

A. *Plan of the study*

1. *Evolution of the test procedure.* Preliminary studies were first made to assess the validity of strontium as a tracer of bone uptake of calcium, and to evolve a method of analysing the results. Then a clinical survey of the test was begun in various patients, during which it was determined whether the serum and urine curves showed a definable 'phase 2' of exponential pattern. Finally faecal losses of strontium were measured in some of these patients, to see whether they would significantly affect the results; for obviously the test would be simpler if this measurement were not needed.

TABLE I

Patients Studied by the Strontium Test

	Tests	*Patients*
Normal subjects	15	13
Hyperparathyroidism	17	9
Steatorrhoea	27	17
Thyrotoxicosis	18	16
Hypoparathyroidism	8	6
Chronic jaundice	11	7
Sarcoidosis	10	7
Invasive bone disease	7	5
Cushing's syndrome	8	6
Osteoporosis	25	21
Renal calculi (idiopathic)	5	5
Hypothyroidism	4	3
Miscellaneous	17	17
Total	172	132

2. *Clinical survey of the diagnostic uses of the test.* When the test procedure had been validated by these studies, a wider survey was undertaken of the clinical usefulness of the test for the diagnosis of metabolic bone disease. For this purpose 132 patients were given 172 tests, with the procedure described below; some of these patients have been reported previously (Fraser, 1957). For analysis of the test results patients were grouped by the clinical diagnosis, made on standard criteria independently of the strontium tests (Table I).

B. *Test procedure*

To minimize any dietary effects, which may be important (Thomas, Litovitz, and Geschickter, 1954), and to permit comparison of results between patients, each patient receives a standard diet of low calcium content, approximately 150 mg. per day, to which calcium lactate tablets are added to bring the total daily calcium intake to 7 mg. per kg. body weight. This level was chosen as the lowest intake possible without a state of negative calcium balance in a normal

subject. No restrictions are placed on the activity of the subjects, other than those necessary on account of their general condition. After three or more days of the fixed calcium intake, patients are given 10 m-equiv. of strontium by intravenous injection, in the form of a 6 per cent. solution of strontium gluconate (Sandoz), preliminary tests having shown this to be a convenient dose. After the injection blood samples are taken at 12-hour or 24-hour intervals for the next 84 hours for estimation of the strontium content. Urine is quantitatively collected for each 24-hour period after administration of the strontium dose, for six or seven days. To each urine collection is added 10 ml. of concentrated HCl to retain the strontium in solution and prevent loss by precipitation. When faecal strontium is to be estimated, faeces are collected for two consecutive three-day periods, the strontium being given on the first day. A few patients have received serial strontium tests at intervals, in order to assess the results of treatment or to study the progress of their disease. In these patients the basal levels of strontium in blood and urine were estimated before the next dose was given, and any strontium detected in these specimens allowed for in the subsequent calculations.

C. *Estimation of strontium*

1. *Serum.* To 1 ml. of serum are added 1 ml. of 0·5 N ammonium oxalate and 0·05 ml. of 10 per cent. calcium gluconate (Sandoz). Calcium and strontium are precipitated as oxalates, and after centrifuging the supernatant is discarded. The precipitate is dissolved in 2 ml. 0·6N HCl, and the final dilution made to one in four by adding 2 ml. distilled water. The solution is sprayed in the photometer, together with standards containing the same amount of calcium, HCl, and oxalic acid, as well as the specified quantity of strontium.

2. *Urine.* (1) The same principle is employed after adjusting the pH to between 5 and 6: that is, the strontium is precipitated together with a known excess of calcium as oxalate, and the centrifuged precipitate dissolved in HCl. This solution is sprayed against suitable standards. (2) For the first 24-hour collection, which contains a relatively large amount of strontium, a more rapid but slightly less accurate method is used. 1 ml. of urine is added to 9 ml. of a KH_2PO_4–$HClO_4$ mixture, as described for the estimation of calcium by MacIntyre (1957), and the diluted urine sprayed against standard strontium solutions similarly prepared.

In some of the earliest tests serum strontium levels were also estimated by adding 1 ml. of serum to the KH_2PO_4–$HClO_4$ mixture, but this method was later discarded in favour of the oxalate precipitation method described above, which is more sensitive.

3. *Faeces.* The three-day faecal pool is homogenized in a mixer, and a sample dried and ashed. A preliminary estimate of the calcium content is first made (so that additional calcium can be added for a constant calcium content). The ash is dissolved in HCl, the pH adjusted to between 5 and 6, and the strontium together with excess calcium precipitated as the oxalate, as for estimation of the urine strontium.

D. *Calculation of results*

The serum concentrations of strontium, the total urinary excretion, and the body retention, at the end of each 24-hour period, are plotted semilogarithmically against time (Fig. 2). After 84 hours the serum levels are usually too low to be measured accurately, but the urine levels, and so also body retention, may be estimated for six or seven days after injection. Each of these parameters shows an initial rapid fall, followed after about 30 hours by an exponential fall

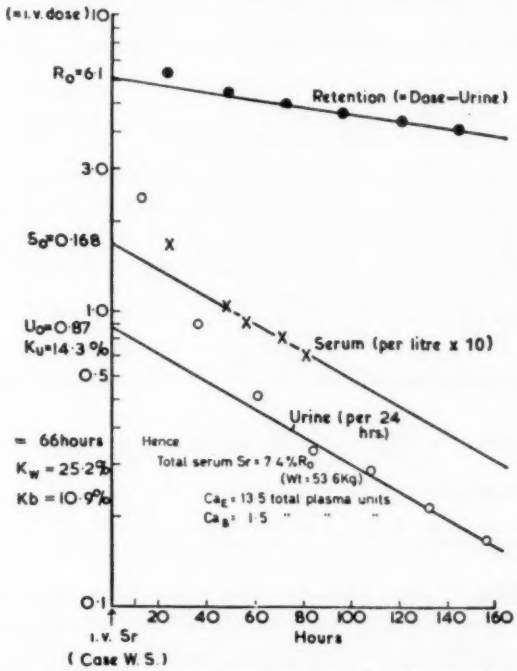


FIG. 2. Sample strontium test results: the calculation of exchangeable calcium (Ca_E) and daily deposited calcium (Ca_B).

(that is, the plotted points lie on a straight line). We have assumed that the initial rapid fall represents the mixing phase, during which the strontium is reaching equilibrium throughout the components of the exchangeable mass. During this time, therefore, the serum level, and so also the urinary loss of strontium, will be disproportionately high. Consequently, had instantaneous mixing been possible, the same levels on the later part of the curves could have been attained from a smaller dose—the 'theoretical dose'. This 'theoretical dose' is first determined by extrapolating the line joining the serial points of the exponental phase of the curve representing body retention back to zero time; this intercept on the y-axis indicates the theoretical dose or effective retention of the test (R_o, or theoretical retention at t_o). Similar extrapolation of the

serum and urine lines to zero time gives respectively the serum strontium level per litre (S_o) and the urine excretion per 24 hours (U_o) to be expected when the body contains these R_o units of strontium fully mixed throughout the exchangeable space. In practice the slope of these lines is best defined from the more accurate urine values; and the serum line is the best line which is parallel to this and also passes through the serum points from 48 hours onwards. The corresponding total serum strontium (S_{ot}) is calculated by multiplying S_o by 5 per cent. of the body weight in kg. Then, as strontium and calcium are treated identically by the skeleton, $\frac{R_o}{S_{ot}}$ gives the ratio of the exchangeable calcium mass to the total plasma calcium, or the exchangeable calcium mass in total plasma units.

$$Ca_E = \frac{R_o}{S_{ot}} = \frac{R_o}{S_o} \times \frac{20}{\text{body weight in kg.}} \text{ in total plasma units.}$$

The next step, the measurement of the slope of the serum and urine lines, then permits the derivation of the rate of calcium deposition in bone (Ca_B). The half-life of this slope in days ($t_{\frac{1}{2}}$) is converted to the corresponding percentage rate (K_w), or the daily percentage loss of calcium from the exchangeable pool, by the standard formula $\left(K_w = \frac{0{\cdot}693 \times 100}{t_{\frac{1}{2}}}\right)$.

From the extrapolations we have $\frac{U_o \times 100}{R_o}$, or K_u, the percentage of Ca_E lost daily into the urine; so $\left(K_w - \frac{100U_o}{R_o}\right)$ will give the residual percentage loss of Ca_E into bone (K_b).

Therefore $Ca_B = \frac{(K_w - K_u)}{100} \times Ca_E$ in total plasma units.

If desired, either of these final estimates (Ca_E or Ca_B) may be expressed in mg. of calcium by multiplying these values in total plasma units by the estimated total serum calcium (serum Ca in mg. per litre $\times$ 5 per cent. of body weight in kg.). The values of K_u have ranged in normal subjects from 7 per cent. to 32 per cent., and the ratio of $\frac{K_w}{K_u}$ from 1·3 to 3·2.

Results

I. *Preliminary assessment*

1. *The validity of strontium as a tracer of the skeletal turnover of calcium.* Fig. 3 shows the results of 17 combined calcium and strontium infusions, carried out as described for calcium by Finlay, Nordin, and Fraser (1956), but prolonged to provide 24-hour measurements of strontium. There is a good correlation between the four-hour calcium space and the 24-hour strontium space (see note to Fig. 3), the two most appropriate indices obtainable from such a short test ($r = 0{\cdot}88 \pm 0{\cdot}06$; $Ca_{4\,hr.} = 0{\cdot}59 \times Sr_{24\,hr.} - 1{\cdot}1$). The comparison has been

made between these two figures, since this 'calcium excess' procedure cannot validly be applied later than the end of the infusion, at four hours, after which the serum calcium rapidly returns to normal; while the 24-hour strontium space is the 'space' estimate which correlates best with the indices derived from the longer standard strontium test (Ca_E+Ca_B; see below). These infusions also demonstrated that the urinary clearance of strontium is about three times that

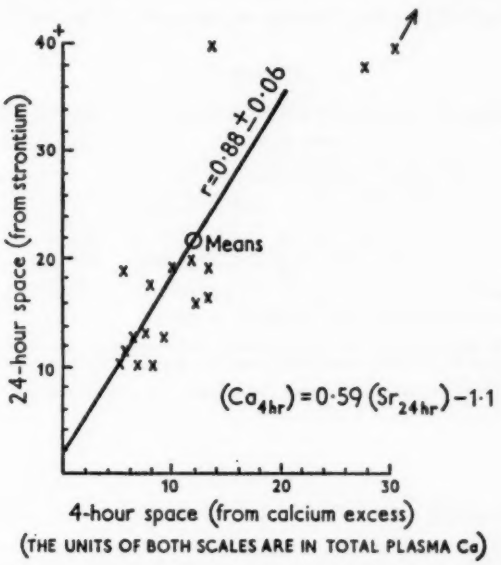


FIG. 3. Seventeen combined calcium and strontium infusions: the correlation of 24-hour strontium space and four-hour calcium space.

The calcium 'space' in litres of plasma = the total body retention of the infusion divided by the excess calcium found at the same time per litre of plasma. The serum excess calcium = the calcium concentration at four hours after starting the infusion minus the calcium concentration before infusion.

of calcium. This finding confirms those obtained from comparable studies in man (Harrison, Raymond, and Tretheway, 1955; Comar, Wasserman, and Nold, 1956; Spencer, Brothers, Berger, Hart, and Laszlo, 1956; Spencer, Laszlo, and Brothers, 1957; Bauer and Ray, 1958); but, as this urinary loss does not influence the skeletal handling of the two elements, it does not affect the validity of strontium as a tracer for calcium in this test.

2. *The effect of the dosage of strontium.* Five normal subjects each received two to four serial strontium infusions (14 in all) in doses ranging from 0·05 to 0·15 m-equiv. Sr per kg. body weight. The 24-hour space measurements so obtained did not vary with the dose of strontium, and so strontium may be regarded as a tracer at the dose level recommended. When the 24-hour space measurements were first expressed as a percentage of the mean 24-hour space

in each subject, and then summed in four groupings of strontium dosage, these final mean values lay between 94 and 101 per cent.

3. *The consistency of a measurable exponential phase.* Fig. 2 shows an example of the measurements obtained from one test, and is representative of the closeness of the observed points to the derived lines in the majority of the tests.

4. *The significance of the faecal loss of strontium.* Clearly the standard test procedure, by ignoring the faecal loss, will overestimate the rate of bone turnover by the extent of this loss, though its estimate of the exchangeable calcium

TABLE II*a*

Strontium Tracer Test: The Significance of Faecal Excretion

Group and number of patients	*Faecal strontium*		*Estimate of rate of bone deposition of Ca (total plasma units/day)*	
	Percentage of intravenous dose in 0–6 days	*Implied rate of loss from plasma (total plasma units/day)*	*(a) Standard procedure*	*(b) Corrected for faecal loss*
Steatorrhoea (4) .	20·6 (8·8–32·5)	1·47 (0·85–2·80)	5·05 (3·20–6·50)	3·55 (2·0–5·45)
Osteoporosis (6) .	11·2 (8·6–14·8)	0·43 (0·27–0·53)	1·35 (0·80–1·60)	0·90(0·35–1·80)
Miscellaneous with normal absorption (8)	11·3 (8·3–16·6)	0·43 (0·16–0·66)	1·85 (0·55–3·10)	1·30 (0·40–2·60)
Normal range (using mean faecal correction from last two groups)			..	0·85 (0·35–1·55)

The true retention in deep bone by the 5th day (B) = the strontium dose minus the sum of faecal Sr excretion over 0–6 days (F), urinary Sr excretion over 0–5 days, and the strontium in Ca_B at the 5th day $\left(R_0 \times \frac{\text{serum Sr at 5th day}}{\text{serum Sr at } t_0}\right)$; then, Ca_B corrected for faecal loss = standard $Ca_B \times \frac{B}{B+F}$.

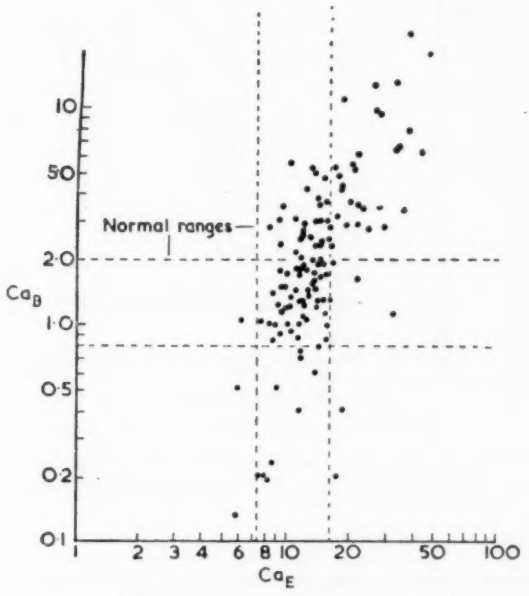
TABLE II*b*

Faecal Strontium after Intravenous Administration: Other Estimations

	Dose of strontium (Sr)	*Time in days*	*% dose in faeces*	*Subject*	*Authors*
1.	100 mg.	30	6	Normal	Harrison, Raymond, and Tretheway (1955)
2.	20 mg.	30	0	Normal	,,
3.	^{85}Sr 0·1–0·4 μc/kg.	12	10·4	Carcinoma of bronchus	Spencer, Laszlo, and Brothers (1957)
4.	^{85}Sr 0·1–0·4 μc/kg.	12	12·7	Lymphoma + osteoporosis	,,
5.	^{85}Sr 0·1–0·4 μc/kg.	12	14·2	Senile osteoporosis	,,
6.	^{85}Sr 0·1–0·4 μc/kg.	12	6·5	Paget's disease	,,

mass should not be affected. Although it seemed likely that the faecal loss would be small and constant, so that the test would be clinically valid without allowing for it, we felt it necessary to be certain of this, particularly in conditions of malabsorption. The faecal loss of strontium over the first six days was therefore measured in 18 of the tests, and the results are shown in Table II*a*. Included among the 18 patients were four with defective intestinal absorption (steatorrhoea) and six with a suspected decrease of bone deposition (osteoporosis)—the groups in which this source of error might be serious. As will be seen in Table II*a*, about 11 (8 to 16) per cent. of the injected strontium appeared in the faeces when intestinal absorption was normal; this implies a daily faecal loss of 0·43 (0·16 to 0·66) 'total plasma calcium units'. Table II*b* shows that estimates of the faecal

output of intravenously injected strontium are in good agreement with our own. This daily faecal loss is estimated by the standard test procedure as turnover in bone, which is therefore overestimated by about 0·43 total plasma calcium units, or about 30 per cent. of the value in normal subjects. In the four patients with defective intestinal absorption this faecal loss varied more, and was higher (the mean being twice that found in the other cases); but in



(BOTH SCALES ARE IN TOTAL PLASMA UNITS)

FIG. 4. The correlation between Ca_E and Ca_B in 128 strontium tests.

these patients the daily bone turnover of calcium was found to be even further increased, so that none of the turnover values were abnormally high solely because of an increased faecal loss. On the other hand, this loss was not found to be excessive in osteoporosis, and had not masked an abnormally low bone turnover of calcium. We have concluded from these results that it is clinically valid to ignore the faecal loss in this test, allowing it to cause a moderate but fairly constant overestimate of the daily bone turnover of calcium—as it were, a constant 'blank' addition to all estimates.

5. *Interpretation of the test results.* Fig. 4 shows the relation between the two indices of the test, Ca_E and Ca_B, and indicates that changes in one tend to be associated with similar changes in the other. In some cases, however, only one of these indices is abnormal, usually Ca_B. If mixing were nearly completed by 24 hours, the 24-hour Ca mass (or 'space') should equal the sum of these two indices of bone turnover, and thus provide a short method for the test. Fig. 5 shows that this 24-hour mass does give a good approximation to the sum of Ca_E and

Ca_B; a 'Ca-avidity index'. This index has the disadvantage, however, of not revealing any irregularities in the collection of urine or in the strontium estimations, as does the longer test, and of not giving separately the more sensitive Ca_B index.

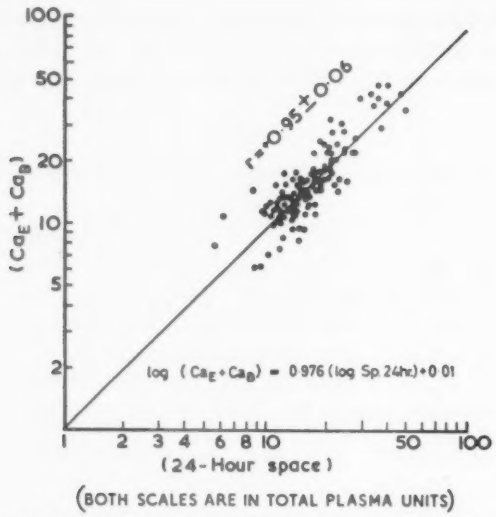


FIG. 5. The correlation between (Ca_E and Ca_B) and 24-hour strontium space in 128 strontium tests.

II. *Results in normal subjects*

Table III shows the results obtained in 15 tests in normal subjects, including six staff volunteers. All these subjects were adults, and with our small numbers we have been unable to derive a correction for age; but such a correction doubtless would be appropriate particularly before maturity (Bauer, Carlsson, and Lindquist, 1957). The distribution of the Ca_E and Ca_B values in these subjects is slightly skewed towards the higher values, but the distribution of the corresponding log values appears approximately normal, and has been used, therefore, to define the normal ranges.

III. *Results in disease*

A. *Conditions showing increased bone turnover of calcium*

1. *Hyperparathyroidism* (Fig. 6 and Table IV). All the nine hyperparathyroid patients tested showed increased rates of bone turnover of calcium (Ca_B), and seven also showed an increased exchangeable calcium mass (Ca_E). Among these patients are included two who had radiologically normal bones (HW 663 and AL 743), and whose disease had been discovered after the incidental finding of nephrocalcinosis in one case, and renal calculi in the other, during the investigation of hypertension; and another patient in whom the only radiological evidence of bone disease was a single localized cyst (BC 565). The

test findings are of considerable diagnostic significance in the presence of definite or suspected hypercalcaemia; since, as noted below, other patients with hypercalcaemia were found to have normal rates of bone turnover of calcium (in secondary malignant invasion of bone, myeloma, the milk-alkali

TABLE III

Strontium Tracer Test: Normal Subjects

Subject	Test number	Age (years)	Sex	Weight (kg.)	Diagnosis	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
3.RF	336	48	M	79	Chosen normal	11·8	1·7	9·9	156
4.RF	411	,,	M	79	,,	13·7	1·2	11·2	216
1.ML	341	27	F	59	,,	11·5	1·3	10·2	116
2.EE	337	34	M	70	,,	9·35	1·8	10·4	..
4.EE	408	,,	M	68	,,	11·0	1·45	10·7	222
3.AD	412	29	F	64	,,	11·4	1·0	11·1	162
1.JR	400	49	M	53	Abdominal pain	16·2	1·3	10·7	292
1.OA	413	46	F	57	Idiopathic oedema	10·2	1·2	9·2	66
1.GS	414	30	F	56·5	Hyperventilation tetany	9·2	0·9	10·2	129
1.ES	561	43	F	51·5	Gastrectomy	12·0	1·25	9·6	117
1.JG	566	42	M	71	Urticaria pigmentosa	12·4	1·05	11·1	198
1.GB	606	62	F	52·5	Rheumatoid arthritis	16·3	1·85	11·3	192
1.JH	611	40	M	57·5	Pneumonia	13·4	1·0	10·0	..
1.SM	638	17	F	61	Chosen normal	12·8	1·5	10·8	206
1.LS	639	26	F	61·5	,,	6·6	1·2	10·6	72
Mean (of 15)		..	..	62·8	..	11·5 (median 11·8)	1·3 (median 1·25)		
95 % probability range		..	..	..	..	7·3–16·8*	0·8–2·0*	..	..

* Calculated from mean ±2 S.D. of log values.

TABLE IV

Strontium Tracer Test: Hyperparathyroidism

Patient	Test number	Age (years)	Sex	Presenting syndrome and therapy	Blood urea (mg./100 ml.)	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) *Untreated*									
1.AA	344	68	F	Bone disease	119	18·8	11·0	16·7	84
1.GT	324	43	F	,,	40	33·6	6·55	15·6	251
1.BC	565	47	F	,,	42	14·2	3·10	15·2	54
1.LC	608	52	F	,,	72	29·2	9·85	13·0	107
1.OB	609	51	F	,,	24	28·0	6·65	14·3	500
2.OB	645	,,	,,	,,	..	28·0	9·50	13·6	298
1.HW	663	67	M	Normal bones	37	21·9	3·55	13·6	200
1.HC	739	58	F	Bone disease	49	60·2	14·6	16·2	186
1.CA	720	61	F	,,	75	40·2	13·6	14·4	112
1.AL	743	48	M	Normal bones	49	14·3	2·20	12·6	460
(b) *Post-operative*									
2.AA	349	..	..	4 days post-op.	132	26·8	12·8	8·4	20
3.GT	401	..	..	4/12 post-op.	59	61·5	21·0	9·9	8
3.AA	521	..	..	9/12 post-op.	120	20·1	5·25	9·4	26
4.GT	513	..	..	10/12 post-op.	43	34·2	6·75	10·2	10
2.BC	568	..	..	10 days post-op.	58–76	19·6	2·85	9·8	0
2.LC	646	..	..	2/12 post-op.	95	28·0	9·50	7·0	38
3.BC	626	..	..	2/12 post-op.	39	12·3	2·90	11·0	15

syndrome, and sarcoidosis). The same abnormality might possibly be anticipated in vitamin-D intoxication, though we have not tested such a case, but it was not found in hypercalcaemic sarcoid. In several patients the test has been repeated after removal of the parathyroid tumour and correction of the hypercalcaemia. For many months the evidence of an avidity for calcium in the bones persisted. Presumably this is a manifestation of the residual osteomalacia, whose severity will vary with the extent of the original bone disease, and which will only

slowly be corrected as the body's depletion of calcium is made good. Indeed, there is a hint of an increase in the rate of the deposition of calcium in bone immediately after parathyroidectomy. This may reflect an even greater avidity in the bones after the correction of the hypercalcaemia, in order to maintain the same mass of calcium deposition, since our test units are in terms of the calcium in the patient's total plasma, not in milligrams of calcium. The changes may,

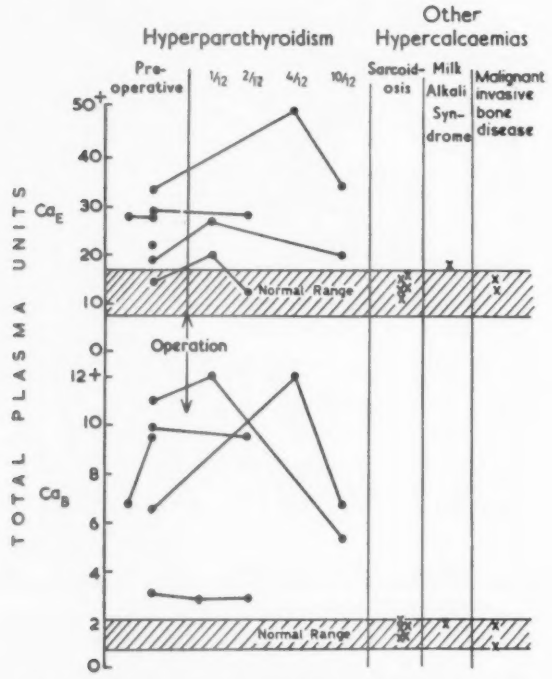


FIG. 6. The differential diagnosis of hypercalcaemia: the strontium test results in hyperparathyroidism and other hypercalcaemic states.

however, not be significant, for the test is less precise with these greatly increased rates, owing to very low levels of urine and serum strontium being estimated. But there is usually a concomitant post-operative rise in plasma alkaline phosphatase, which also suggests such an increased activity of bone deposition.

2. *Osteomalacia and steatorrhoea* (Fig. 7 and Table V). All these patients had steatorrhoea; some had presented symptoms due to the bone disease, but most had other symptoms which led to the discovery of steatorrhoea. They have been grouped for this presentation into those with osteomalacia confirmed by standard radiological or biochemical criteria, those without these features, and finally those of either group who had already been treated with vitamin D. It is evident that in all the untreated patients with definite steatorrhoea (with

or without clinical osteomalacia) the test showed an abnormally rapid turnover of calcium by bone, the values of Ca_B being usually above twice the upper limit of normal, and that many also showed an increased Ca_E. Nearly all tests carried out after treatment with vitamin D had been instituted still showed the same abnormality, but in most cases there was a trend towards normal levels.

TABLE V

Strontium Tracer Test: Steatorrhoea

Patient	Test number	Age (years)	Sex	Diagnosis and therapy	Strontium test (in total plasma units) Ca_E	Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) With osteomalacia, untreated with vitamin D								
1. MP	506	54	F	? Crohn's disease	22·0	6·2	7·0	7
1. LH	528	61	F	Post-gastrectomy	41·0	6·5	8·6	88
1. DC	536	35	F	,, +renal acidosis	15·0	4·85	7·6	55
2. DC	552	,,	,,	Treated with alkalis 11 weeks	23·0	10·0	7·9	82
1. JB	603	16	F	Crohn's disease	27·5	6·35	9·8	16
1. JD	623	54	M	Idiopathic	21·5	4·45	9·2	56
1. VF	637	54	F	Idiopathic	29·0	2·8	8·4	54
1. CM	659	52	M	Post-gastrectomy	22·5	3·45	9·6	53
(b) Without osteomalacia, untreated with vitamin D								
1. BW	520	24	M	Bowel resection	12·5	4·2	10·3	10
1. ST	532	52	M	Idiopathic	20·5	5·6	8·9	20
1. FR	535	46	M	Idiopathic	11·0	3·2	9·5	46
2. FR	540	,,	,,	Treated with cortisone 100 mg. for 10 days	15·5	3·0	10·1	46
(c) Treated with vitamin D								
(i) Less than one week:								
1. CS	415	45	M	Idiopathic	21·5	1·65	10·0	213
2. MP	509	54	F	Crohn's disease	13·5	5·1	8·5	10
2. BW	527	24	M	Bowel resection	9·9	1·0	10·1	5
2. LH	533	61	F	Post-gastrectomy	27·0	5·65	9·3	217
(ii) One week to one month:								
1. LiH	519	72	F	Post-gastrectomy	12·5	2·65	9·5	74
2. VF	654	54	F	Idiopathic	36·5	4·4	9·4	66
(iii) Over one month:								
2. RM	423	28	F	Idiopathic (6 months)	17·0	5·35	9·8	147
3. RM	542	28	F	No therapy for 5 months	27·0	3·5	10·3	150
3. DC	602	37	F	Post-gastrectomy + acidosis (2 months)	29·0	11·0	8·3	42
4. DC	635	,,	,,	,, ,, (5 months)	32·0	11·0	8·0	54
(d) Possible steatorrhoea not confirmed								
1. KM	404	55	F	Post-gastrectomy	11·5	0·4	9·7	193
1. ML	553	26	M	Diarrhoea	16·5	1·95	10·6	210
1. BH	554	18	F	Crohn's disease + resection	16·0	2·85	9·0	124
(e) Treated osteomalacia of uncertain aetiology								
1. MS	358	68	F	Healed osteomalacia and steatorrhoea Ca and vitamin D for 2 yrs.	5·8	0·6	11·0	223
2. MS	670	70	F	Ca but no further vitamin D for 2 yrs.	9·2	1·25	10·2	176

Only one patient has been tested at a time when full restitution of the bone disorder had been achieved, and the test showed normal values. It had, of course, to be considered that the increased turnover found in these osteomalacic bones might merely reflect the increased loss of the injected strontium in the faeces due to malabsorption. But, as noted above (I. §4; Table II*a*), this was not so; while there was increased faecal loss of strontium in steatorrhoea, it accounted for only a small portion of the increased bone turnover found in these patients.

3. *Thyrotoxicosis* (Fig. 8 and Table VI). These cases have been divided on clinical criteria into severe, mild, and treated groups. In the last group have

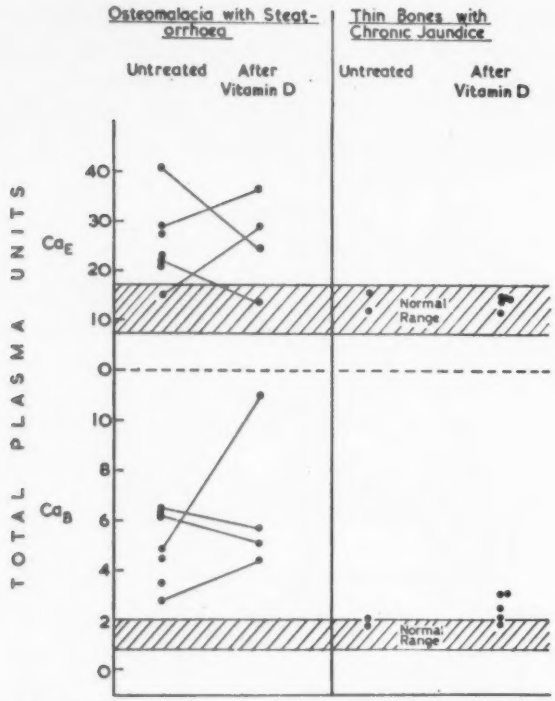


FIG. 7. The strontium test results in osteomalacia and in chronic jaundice.

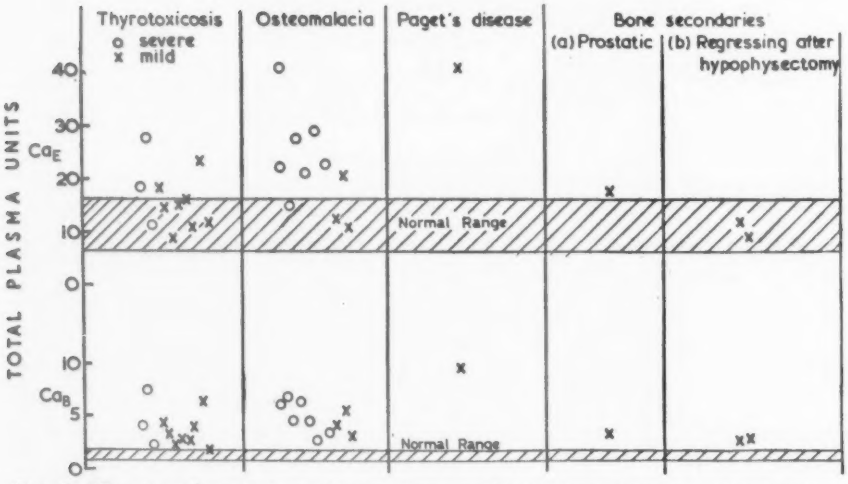


FIG. 8. The strontium test results in 'hypermetabolic' bone disease without hypercalcaemia.

been placed all patients judged at the time of the test to be no longer thyrotoxic. All patients were found to have normal calcium, phosphorus, and alkaline phosphatase values in the blood. It will be seen that all three groups showed an increased turnover of calcium by the bones, which was probably more marked among the severe cases. There was also a high urinary calcium excretion in two of the 10 severe cases, and in two tests on one patient in the group of milder cases who was also receiving cortisone. It is of interest that in the treated patients the bone avidity has persisted up to two years after final correction of the thyrotoxicosis. It is probable that this depends on the considerable time necessary to restore the skeletal calcium, as was also found in the hyperparathyroid patients after treatment.

TABLE VI

Strontium Tracer Test: Thyrotoxicosis

Patient	*Test number*	*Age (years)*	*Sex*	*Complications*	*Antithyroid therapy*	*Duration of disease*	*Strontium test (in total plasma units)* Ca_E	Ca_B	*Mean urine Ca (mg./24 hrs.)*
(*a*) *Severe*									
2.DH	352	42	M	Thin bones and myopathy	5 months	21 months	18·1	4·3	98
1.AP	356	63	F	,,	Few days	4 years	8·5	2·35	55
1.TC	402	52	M	,,	,,	10 months	18·2	4·05	143
1.LK	562	53	F	Thin bones	5 months	6 years	16·1	2·8	64
1.VD	627	50	F	Myopathy	,,	18 months recurrence	23·4	6·1	110
1.FT	634	57	M	..	..	6 months	11·2	2·3	182
1.JDP	633	40	M	Thin bones and myopathy	..	,,	27·8	7·4	356
1.CP	686	74	F	,,	..	1–2 years	41·0	9·15	95
1.SW	693	54	F	Thin bones	..	6 months	19·1	6·6	132
1.FC	694	56	M	Thin bones and myopathy	Few days	12–18 months	14·8	1·4	330
(*b*) *Mild*									
1.CC	556	47	F	Severe exophthalmos	3 months (also cortisone)	4 months	15·1	3·0	430
2.CC	630	47	F	,,	8 months (+4 months cortisone)	9 months	14·1	2·8	324
1.EC	605	56	F	..	..	1 year	10·9	3·9	216
1.CJ	630	37	F	..	17 years (irregular)	17 years	11·8	1·8	60
1.WC	717	64	F	Thin bones	15 years (irregular)	15 years	14·3	2·3	83
(*c*) *Formerly toxic, now euthyroid*					*How long euthyroid*				
3.DH	426	43	M	1 year; formerly severe, with thin bones			18·0	4·4	117
1.MP	345	59	F	2 years;	,,		9·15	3·05	62
1.RB	357	23	M	3–6 months; formerly severe			14·3	3·6	72

4. *Other conditions* (Fig. 8). Increased turnover of calcium by the bones was also found in some other patients: for example, one with osteosclerotic metastases in bone from a prostatic carcinoma (ST 616); one with Paget's disease of bone (HG 625); and one with bone metastases from breast carcinoma, which were regressing after hypophysectomy (MM 504 and 511).

B. *Conditions showing a normal bone turnover of calcium*

1. *Hypoparathyroidism* (Table VII). We have tested only one patient in the untreated state, a woman of 32, who also had osteoporosis with vertebral fractures discovered at the end of pregnancy. Both these conditions may have contributed to her low turnover rate, but Heaney and Whedon (1958) also found a low rate in a patient with uncomplicated hypoparathyroidism. Six

months after starting calciferol therapy the rate was still low in our patient. The other patients were tested after treatment with calciferol or dihydrotachysterol. Two of these patients showed a very rapid bone turnover, but they had recently had thyrotoxicosis, and probably this rapidity was a residual manifestation of the thyroid disease, so that no simple effect from the hypoparathyroidism can be discerned. The other treated patients showed normal results.

TABLE VII

Strontium Tracer Test: Hypoparathyroidism

Patient	Test number	Age (years)	Sex	Presenting syndrome and therapy	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
1. LP	514	53	F	Post-operative (Hashimoto); vitamin D 5 yrs.	11·9	1·9	6·0	49
1. MS	334	32	F	Idiopathic untreated +osteoporosis	13·7	0·6	6·2	12
2. MS	419	,,	,,	Vitamin D 6 months	5·8	0·55	10·4	57
1. EP	350	49	F	Post-operative (thyrotoxicosis); vitamin D 6 months	12·2	1·4	9·4	94
1. JM	613	18	F	Post-operative (thyrotoxicosis); dihydrotachysterol 2 weeks	52·5	9·2	9·2	67
2. JM	619	,,	,,	Vitamin D one week	46·5	6·3	10·7	306
1. AM	668	63	F	Post-operative (thyrotoxicosis); vitamin D 8 yrs.	8·9	1·2	8·0	48
1. GB	551	26	M	Post-operative (thyrotoxicosis); dihydrotachysterol 3 days	27·7	12·2	6·7	41

TABLE VIII

Strontium Tracer Test: Chronic Jaundice

Patient	Test number	Age (years)	Sex	Duration of vitamin-D therapy	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) Not treated with vitamin D								
(i) +Thin bones								
1. HC	329	35	F	..	11·95	2·0	10·2	106
1. RG	629	40	F	..	15·5	1·85	9·8	63
(ii) Normal bones								
1. EK	558	31	M	..	16·2	2·3	9·8	168
(b) Treated with vitamin D								
+Thin bones								
1. DH	351	53	F	1 day	13·9	3·0	10·1	42
1. MB	407	70	F	2 weeks	14·9	2·4	9·4	..
2. MB	410	,,	,,	4 weeks	8·95	0·55	10·5	..
1. JE	333	45	F	4 yrs.	14·85	2·05	10·1	66
2. JE	522	46	,,	5 yrs. vitamin D stopped	15·7	2·5	9·8	122
3. JE	530	,,	,,	5 yrs. vitamin D restarted (on cortisone)	10·4	5·6	8·7	23
2. DH	544	54	F	1 yr.	11·8	1·8	9·6	84
1. CM	515	63	F	6 months	14·8	3·0	9·4	123

2. *Chronic jaundice* (Fig. 7 and Table VIII). It is a recognized clinical fact that chronic jaundice leads to the development of bone thinning, with or without fractures, a condition of which the pathogenesis is not easily explained (Atkinson, Nordin, and Sherlock, 1956). It is a notable feature that in the three untreated patients tested the bone turnover of calcium was found to be normal, or nearly normal, in contrast to the findings in osteomalacia. The results were normal, or only slightly increased, in those patients who had begun treatment with vitamin D, but in whom this bone thinning had nevertheless persisted.

3. *Sarcoidosis* (Fig. 6 and Table IX). Those patients who showed hypercalcaemia have been separated from the others; in most of the latter the disease was active and untreated, but in some it was quiescent and probably healed. As indicated in Table IX, some of the patients have been tested while receiving cortisone or prednisolone, as well as before this treatment, or after it had been withdrawn for a period. The striking finding in these patients is a normal skeletal turnover of calcium, an important finding particularly in hypercalcaemic patients, in whom it is important to exclude hyperparathyroidism. One of the patients with normal blood calcium showed a slightly increased turnover of calcium by the bones, for which no explanation was evident.

TABLE IX

Strontium Tracer Test: Sarcoidosis

Patient	Test number	Age (years)	Sex	Presenting syndrome and therapy	Strontium test (in total plasma units) Ca_E	Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) With hypercalcaemia (recent or present)								
1. PM	348	36	F	Untreated	15·0	1·3	12·8	250
2. PM	353	,,	,,	On prednisolone 1 month	15·7	1·7	10·3	128
1. EP	418	28	M	Untreated	12·8	1·35	11·1 (highest 11·5)	406
1. IP	417	59	M	On prednisolone 4 months	13·35	2·0	10·9 (highest 11·5)	147
2. IP	424	,,	,,	Off prednisolone	11·2	1·8	9·9 (recently 14·4)	158
(b) No hypercalcaemia								
1. PO	347	38	F	Healed sarcoid	7·85	0·02	10·4	230
2. PO	354	,,	,,	After cortisone	5·85	0·33	9·9	262
1. AH	500	30	M	Untreated	14·0	1·3	9·6	232
1. DC	507	23	M	,,	21·7	2·85	10·5	264
1. MB	547	32	M	,,	8·9	1·05	9·8	160

TABLE X

Strontium Tracer Test: Invasive Bone Disease

Patient	Test number	Age (years)	Sex	Presenting syndrome and therapy	Strontium test (in total plasma units) Ca_E	Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) With hypercalcaemia (recent or present)								
2. MM	504	39	F	Cancer (breast) in bone; 2 months after hypophysectomy	11·9	2·5	9·4 (pre-op. 15·0)	125
3. MM	511	,,	,,	Cancer (breast) in bone; 3 months after hypophysectomy	8·3	2·85	10·6	106
1. SG	557	53	M	Myeloma	15·3	0·85	12·1	..
1. AC	563	42	F	Cancer (breast) in bone	12·7	1·8	17·2	..
(b) Without hypercalcaemia								
1. DM	537	56	F	? Myeloma	8·4	0·65	9·7	126
2. DM	539	,,	,,	? Myeloma	7·4	0·2	11·3	282
1. ST	616	55	M	Cancer (prostate) in bone	17·0	3·40	9·6	..

4. *Invasive bone disease* (Fig. 6 and Table X). Patients with diffuse or metastatic invasion of bones in this group have been included. Again those who were hypercalcaemic at the time of the test are shown separately. Except in one patient with osteosclerotic prostatic metastases, and one in whom breast metastases were regressing after hypophysectomy (both with normal blood calcium), all the test results showed normal rates of calcium turnover by bone—again an important contrast with hyperparathyroidism or osteomalacia.

5. *Cushing's syndrome* (Table XI). In this category have been included patients who had developed the syndrome from prolonged treatment with

cortisone or allied steroids. In the first subdivision are shown the test results obtained either during steroid administration or in the untreated syndrome,

TABLE XI

Strontium Tracer Test: Cushing's Syndrome and Related Disorders

Patient	Test number	Age (years)	Sex	Presenting syndrome and therapy	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) Untreated Cushing's syndrome or chronic excessive cortisone								
1. EG	501	12	M	Cushing's syndrome (pre-operative)	12·65	1·6	10·4	234
1. KS	624	40	F	Cushing's syndrome (pre-operative)	15·6	1·0	10·2	190
1. JB	621	35	F	Asthma; on cortisone 100 mg./day or equivalent since 18 months	10·95	0·9	10·2	152
1. SM	632	56	M	Polyarteritis nodosa; on prednisolone 30–50 mg./day since 33 months	11·0	2·15	10·6	144
(b) Treated Cushing's syndrome or after excessive cortisone								
2. KS	657	40	F	11 days post-operative; on cortisone 25 mg./day	11·9	1·3	10·0	108
1. RH	614	11	M	Dermatomyositis; 1 week after stopping cortisone (100 mg./day for 21 months)	13·8	3·3	9·8	44
(c) Congenital virilism (pseudohermaphroditism)								
(i) Untreated:								
1. CH	636	24	F	..	10·8	0·75	10·8	215
(ii) *After 10 days' suppression of androgens with fluorocortisol 10 mg./day*								
2. CH	643	24	F	..	8·1	0·2	10·0	316

TABLE XII

Strontium Tracer Test: Osteoporosis

Patient	Test number	Age (years)	Sex	Diagnosis and therapy	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
(a) Untreated (+high urine Ca)								
1. MC	516	65	F	Post-menopausal	13·3	1·55	10·2	193
1. JS	517	54	M	Senile	9·65	1·15	10·0	290
1. LM	538	60	F	Post-menopausal	6·05	1·05	10·6	214
1. RH	543	44	M	Hypogonadism	14·3	0·8	10·0	358
1. RR	550	61	M	Senile	10·0	1·2	9·5	172
1. JD	559	62	M	,,	12·7	2·15	9·9	214
(b) Untreated (+normal urine Ca)								
1. JU	346	70	F	Senile	15·1	1·15	10·8	76
1. BM	403	60	F	,,	11·7	1·5	10·4	13
1. GO	405	39	M	Unknown	13·7	1·6	10·4	82
1. LB	406	64	F	Post-menopausal	9·4	1·6	10·3	71
1. NB	503	64	F	,,	9·1	1·25	10·1	..
1. EH	505	75	F	,,	8·6	1·4	10·2	109
1. HI	529	68	M	Senile	13·7	2·35	9·3	97
1. DW	534	63	F	Post-menopausal	12·1	1·6	10·2	105
1. CW	656	61	M	Senile	12·5	1·45	9·6	..
1. LG	658	61	F	Post-menopausal	10·8	1·30	11·1	143
(c) Treated								
1. EC	525	65	F	Oophorectomy; oestrogens and androgens	9·9	1·55	11·3	134
1. DF	531	32	F	Post-partum; high Ca diet	8·35	1·05	10·2	174
2. LB	546	65	F	Senile; high Ca diet	10·1	1·7	9·0	79
2. NB	600	65	F	Senile	9·15	1·25	9·7	54
3. NB	601	,,	,,	,, +growth hormone	10·2	0·85	10·9	100
(d) Urticaria pigmentosa + osteoporosis								
1. MD	302	39	F	..	10·2	2·65	10·3	144
2. MD	307	,,	,,	High Ca diet	13·3	5·35	9·6	..
(e) Osteogenesis imperfecta								
1. JT	339	11	M	..	17·7	3·2	11·0	184
1. DG	518	26	F	Dwarfism	15·0	1·9	9·8	120

and in the second section some results obtained immediately after cessation of steroid treatment, or after subtotal adrenalectomy for Cushing's syndrome. These results show that the turnover of calcium is within the adult normal

range in this type of adrenal cortical overactivity. The child with Cushing's syndrome (EG 501) should probably have, at the age of 12, a higher turnover rate well above the adult normal, though we have not any test results from normal subjects of this age. After the removal of an overactive adrenal (KS 624 and 657) there may be a slight rise in the turnover rate. Thus there is a hint of a decreased turnover rate in Cushing's syndrome; but the more striking abnormality is the hypercalcuria, which recedes immediately after correction of the hyperadrenalism.

TABLE XIII

Strontium Tracer Test: Idiopathic Renal Calculi

Patient	Test number	Age (years)	Sex	Blood urea (mg./100 ml.)	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
1. HC	628	33	M	33	11·6	0·7	10·4	256
1. JL	640	48	M	30	9·6	1·55	10·0	128
1. WJ	651	47	M	20	9·95	1·0	10·0	218
1. ED	713	59	M	39	8·65	0·1	10·5	346
1. JO	742	46	M	33	13·2	1·85	9·6	239

TABLE XIV

Strontium Tracer Test: Hypothyroidism

Patient	Test number	Age (years)	Sex	Diagnosis and therapy	Strontium test (in total plasma units) Ca_E	Strontium test (in total plasma units) Ca_B	Mean serum Ca (mg./100 ml.)	Mean urine Ca (mg./24 hrs.)
1. EH	416	38	F	Post-operative 6 years. No therapy 3 yrs.	10·8	1·8	10·5	127
1. RK	618	35	M	Spontaneous; untreated	11·6	1·2	11·2	..
1. EB	642	57	F	Post-operative; ^{131}I; 4 yrs. untreated	10·2	1·35	9·1	61
1. SK	737	51	F	Spontaneous; no therapy 3 months	11·2	1·75	10·4	140

6. *Osteoporosis* (Table XII). Twenty-one patients with this condition, mostly of senile or post-menopausal type, have been tested. Only one case, which was complicated by hypoparathyroidism, showed an abnormally low turnover rate of calcium by the bones, and here the parathyroid deficiency might have been a factor. If the 'simple' (senile and post-menopausal) cases are subdivided into those with and without a high level of urinary calcium, the patients with increased urinary calcium tend to show a turnover rate of calcium within the lower normal range, but the other patients do not even show this hint of abnormality. Possibly in the more active cases there is a slight lowering of the rate of calcium turnover; but in the more chronic and stabilized cases the turnover appears to be quite normal.

7. *Renal calculi* (Table XIII). In the five patients, of whom four showed hypercalcuria, conventional biochemical and radiological investigation had excluded hyperparathyroidism and uraemia. Table XIII shows that the bone turnover of calcium was normal in each patient.

8. *Hypothyroidism* (Table XIV). Normal test results were obtained in all four patients. Further observations are needed, since Krane, Brownell, Stanbury, and Corrigan (1956), using ^{45}Ca, found a decreased rate of bone turnover in hypothyroid patients.

9. *Miscellaneous conditions.* Seventeen patients with various conditions, including acromegaly, obesity, and panhypopituitarism, were studied. Normal rates of bone turnover were found in these groups, excepting one case of acromegaly showing a raised rate of bone deposition ($Ca_B = 3{\cdot}4$ plasma units). In a patient with chronic renal failure and uraemic osteodystrophy a greatly increased rate of bone deposition was found ($Ca_B = 6{\cdot}2$ plasma units). Of particular interest are the increased rate of deposition seen in a patient with Paget's disease, and the normal rate in a patient with the milk-alkali syndrome. On other grounds the latter disease may be almost indistinguishable from primary hyperparathyroidism.

Discussion

Intravenous calcium-tolerance tests have previously been used clinically to measure the skeletal avidity for calcium, and have demonstrated an increased turnover in osteomalacia, even in the mildest cases (Nordin and Fraser, 1956). In these tests sufficient calcium must be infused for its disposal to be measured from the consequent 'excess calcium' in urine and serum. After an infusion over several hours the bone uptake is measured, either simply from the body retention (that is, the percentage not excreted in the urine) or from the 'bone uptake' of the infusion (the percentage not found as 'excess calcium' either in the urine or in the serum and extracellular fluid). This 'bone uptake' may also be expressed as a 'calcium space' (see note to Fig. 3). As noted already, we have found that this 'calcium excess' measurement of the early calcium space correlated well with simultaneous estimates of the 24-hour strontium space (Fig. 3); and the latter gives a good index of the sum of the Ca_E and Ca_B, the two indices of skeletal turnover of calcium derived from the longer strontium test (Fig. 5). Clearly, therefore, these calcium-tolerance tests measure the same processes as the strontium test. The strontium test, however, has certain advantages: the intravenous dose of strontium being small, it is quicker, and also safe even in hypercalcaemic patients; further, as the strontium tracer can be measured both more accurately than the 'excess calcium' and for much longer after the injection, it provides more sensitive indices of bone metabolism (Ca_E and Ca_B) than are obtainable from early measurements of bone uptake.

A wide range of tracer studies[1] confirms our own observations that injected strontium is a valid tracer for the bone uptake of calcium, while the renal

[1] Early studies of strontium metabolism in man and animals (for example by Wood and Arnold, 1899; Mendel and Thacher, 1904; Haldane, 1925) suffered from the absence of a sensitive method for measuring this element. In 1941 Pecher showed that the behaviour of radioactive strontium paralleled that of calcium in skeletal metabolism. Its metabolic cycle and rate of bone turnover after an injected dose were found to be identical with those of calcium, though its rates of excretion by the kidneys and intestines are different, when injected either into animals (Pecher, 1941; Greenberg, 1945; Norris and Kisieleski, 1948; Alexander, Nusbaum, and MacDonald, 1956; Bauer, Carlsson, and Lindquist, 1955*b*, 1955*c*; MacDonald, Noyes, and Lorick, 1956) or into man (Harrison, Raymond, and Trethewey, 1955; Comar, Wasserman, and Nold, 1956; Schulert, Charles, Eckelmann, and Laszlo, 1956; Spencer, Brothers, Berger, Hart, and Laszlo, 1956; Van Dilla and Arnold, 1956; Spencer, Laszlo, and Brothers, 1957; Bauer and Ray, 1958); or when tested *in vitro* on excised bone (Pecher, 1941; Lawrence, 1942; Lengemann, 1957).

clearance and intestinal excretion of an injected dose of strontium are higher than those of calcium. These differences do not matter in this test, which measures the bone turnover of strontium and calcium. The analysis of the tracer data is by standard methods, and based on the simplest likely scheme of calcium movements within the body. This simple basic concept of an exchangeable pool or mass, from which there is a steady loss of calcium into deep bone and excretions, is justified from the simple exponential fall of the decay curves from the second or third to the sixth day. Similar curves during this phase have also been observed in man after injections of ^{85}Sr (Bauer and Ray, 1958) or ^{45}Ca (Krane, Brownell, Stanbury, and Corrigan, 1956; Heaney and Whedon, 1958). It has been shown above that omitting to correct for faecal losses does not involve the test in any clinical errors, even in steatorrhoea.

Our ranges of values for the exchangeable mass (Ca_E) and the rate of bone deposition of calcium (Ca_B) in adults have been based on 15 tests. Bauer, Carlsson, and Lindquist (1957) have published similar tracer data, obtained from 14 probably normal persons, using ^{45}Ca, and conversion of their estimates of Ca_E and Ca_B into total plasma units reveals a similar range for their adult subjects (Ca_E = 12·4 to 22·8; Ca_B = 0·96 to 2·6). Calculations from other published calcium tracer (^{45}Ca, ^{85}Sr) data on human beings have also yielded similar ranges of normal values (Bauer and Ray, 1958; Ca_E = 12·6 to 16·9 and Ca_B = 1·19 to 1·27 total plasma units), and similar ranges have been derived from the data of Geissberger (1951) and Krane, Brownell, Stanbury, and Corrigan (1956). For growing subjects, however, higher values should be expected. Bauer, Carlsson, and Lindquist (1957), using ^{45}Ca, have found considerably higher values in babies (ages one month to one and a half years; Ca_E = 46 to 31 and Ca_B = 13 to 4·9 total plasma units, the values falling from the youngest to the oldest). Similar calculations from the mean data of Bronner, Harris, Maletskos, and Benda (1956), obtained with ^{45}Ca in adolescent boys, showed a Ca_E value in the adult range (9·2 total plasma units), but a higher Ca_B value of 4·4 total plasma units. Clearly the normal range for subjects before maturity will be different, and will require some allowance for age during the period of growth. It is likely that there should also be some corresponding but smaller correction for age over the adult range, but the available data indicate that it can only be small and may be clinically unimportant. It may possibly be of the same order as the corrections for the basal metabolic rate and the radio-iodine test of thyroid function (Macgregor and Wagner, 1958).

On theoretical grounds it was anticipated that the Ca_E estimate of the tracer test would indicate the proportion of young, readily exchangeable bone in the skeleton, for it is known that the young bone in a skeleton contains more water (Neuman and Neuman, 1953) and also receives isotope deposits more rapidly (Thomas, Litovitz, Rubin, and Geschickter, 1952; Tutt, Kidman, Rayner, and Vaughan, 1952; Jowsey, Rayner, Tutt, and Vaughan, 1953). Thus increase in the Ca_E would depend not only on an increased rate of calcium deposition in bone, but also on the duration of the disorder. The data show clearly the advantage of separate estimation of these two indices, Ca_E and Ca_B. In many

of the milder examples of 'hypermetabolic bone disease', for example, in thyrotoxicosis and steatorrhoea (Fig. 8) only the Ca_B is found to be abnormal. Thus it appears that the Ca_B is more sensitive to lesser grades of abnormality than Ca_E. In rare cases, however, abnormality has been evident only in the Ca_E, as for example in CS 415, a very wasted patient with steatorrhoea, who was tested during an acute exacerbation, when new bone formation may have been in abeyance. There are also indications that Ca_E is an index of the total amount of young bone. For example, the patient DC was first tested when her osteomalacia (due to steatorrhoea and renal acidosis) was complicated by severe malnutrition and pyelonephritis. In the early months of treatment there was a striking improvement in her general condition, and along with this there occurred a rise in both Ca_B and Ca_E values. The former index may reflect increased bone deposition following this improvement, and the latter its provision of more new bone.

There is little question of the need for a more sensitive test of calcium metabolism, particularly for the diagnosis of primary hyperparathyroidism, and also for the recognition of subclinical osteomalacia, either in obscure cases of bone thinning or in patients with steatorrhoea or other potential causes of osteomalacia. The strontium tracer test should provide a different index of these metabolic abnormalities, as well as a more sensitive one than the blood level of calcium, or the urinary or faecal excretion of calcium determined in balance tests. The main outcome of the clinical survey with this tracer test has been the discovery that it can delineate a group of clinical disorders characterized by a rapid bone turnover of calcium, a group which may therefore be termed 'hypermetabolic bone disease'. Within this group there are two main sub-groups: the hypercalcaemic cases, all of which are apparently examples of primary hyperparathyroidism, and the cases with normal or decreased blood calcium, mainly comprising osteomalacia and thyrotoxicosis, but also including some other hyperplastic bone conditions such as osteosclerotic metastases, Paget's disease, and malignant invasion of bone which is responding to treatment such as hypophysectomy. These last conditions are readily distinguished from osteomalacia by other clinical criteria, so that the test should have diagnostic value in cases where osteomalacia is suspected. The finding of an increased bone turnover of calcium without hypercalcaemia would be anticipated in bone disorders involving an increased rate of bone formation, that is, in osteosclerotic prostatic metastases in bone, Paget's disease, and malignant metastases regressing after hypophysectomy; and a similar finding in thyrotoxicosis is not unexpected. In osteomalacia, where the bones become thin from inadequate calcification of the bone matrix, this result may seem surprising; but it is consistent with the fact that the serum alkaline phosphatase is generally increased, and also that secondary hyperparathyroidism is usually present in osteomalacia (Salvesen and Böe, 1953). We have already seen that primary hyperparathyroidism is regularly associated with an increased rate of bone deposition, and it seems likely that secondary hyperparathyroidism would be similarly associated. Our results suggest that secondary hyperparathyroidism is a universal feature of

osteomalacia, and indeed that this test may reveal it before the serum levels are abnormal.

In osteoporosis the rate of bone deposition is normal, though in active cases with hypercalcuria, and in the most severe examples of Cushing's syndrome, it tends to be in the lower part of the normal range. This finding does not appear to be in agreement with the classical theory that osteoporosis results from deficient formation of bone matrix. On the other hand, it may be merely confirmatory of the view that the primary disorder is not one of calcium metabolism. Thus the defective matrix may be normally calcifiable, but defective in its retention of calcium, so leading to a gradual bone atrophy. The finding of a normal bone turnover of calcium in chronic jaundice with thin bones was similarly not anticipated. It is in striking contrast with the consistent finding of a rapid skeletal turnover of calcium in all the cases of osteomalacia, and indeed in all the other cases of steatorrhoea tested. Yet these patients did have steatorrhoea, and probably osteomalacia as well (Atkinson, Nordin, and Sherlock, 1956). This finding suggests that the skeletal disorder in chronic jaundice is not simply osteomalacia, but is also complicated by some other condition, perhaps osteoporosis.

An important finding in the test has been the normal turnover in those hypercalcaemic states which might be confused with hyperparathyroidism, namely hypercalcaemic sarcoidosis, the milk-alkali syndrome, and malignant invasion of bone. Among the hyperparathyroid patients tested were two without any clinical or radiological evidence of generalized bone disease, so that a wider survey of hyperparathyroid patients may confirm the test findings as an important diagnostic sign. In the small group of cases of 'idiopathic' hypercalcuria with renal stones the test results were normal. In the hyperparathyroid patients tested after operation the abnormality has persisted for many months, though without any hypercalcaemia. Both in these disorders and in the other 'hypermetabolic bone diseases', after the cause of the abnormality is corrected, the abnormal bone metabolism of calcium as shown by the test is only gradually restored, doubtless because a severe calcium depletion is only replaced slowly. This preliminary survey, therefore, suggests that the strontium tracer test is of value in the diagnosis of hyperparathyroidism, and also of osteomalacia. It should also provide useful data concerning the metabolism in various disorders with skeletal manifestations.

We wish to express our gratitude to Dr. Eugene Eisenberg, who was responsible for carrying out the earlier tests in this series. We also thank Miss Myra Low, Mrs. Ann Ross, and Mrs. Barbara Coates, who carried out the strontium estimations; the Sister and Staff of the Metabolic Ward, Hammersmith Hospital, who supervised the tests; Dr. I. MacIntyre for advice on strontium determination; and Messrs. Sandoz, Ltd., who generously supplied the strontium gluconate.

Summary

1. A clinical method is described for estimating the rate of skeletal deposition of calcium, using stable strontium as a tracer. After an intravenous dose of 10 m-equiv. of strontium, its concentration in the urine and in the serum is measured over the next six days. From the rate of decline of these strontium concentrations it is possible to calculate the rate of movement of this element out of the body fluids into urine and bone. Thus two indices are obtained: (1) the exchangeable calcium mass (Ca_E), and (2) the rate of deposition of calcium in bone (Ca_B), the latter being the more sensitive index of skeletal avidity for calcium.

2. The results of 172 tests in 132 subjects are reported; the normal values being defined from 15 subjects (for Ca_E 7·3 to 16·3, and for Ca_B 0·9 to 2·0 total plasma units). The rate of skeletal deposition of calcium was found to be increased in: (1) all of nine patients with primary hyperparathyroidism, while it was normal in all other hypercalcaemic states tested; (2) 16 out of 17 patients with osteomalacia or steatorrhoea tested, including those without the usual clinical evidence of osteomalacia; (3) a few other conditions, readily distinguishable by other means, viz. thyrotoxicosis, Paget's disease, and healing carcinomatosis of bone.

3. The test is recommended as an aid to the diagnosis of suspected primary hyperparathyroidism or osteomalacia, and also for assessing the effect of treatment on certain bone diseases.

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FIG. 1. A common carotid arteriogram demonstrating a complete obstruction of the internal carotid artery just distal to its origin. The external carotid artery and its branches are filling normally

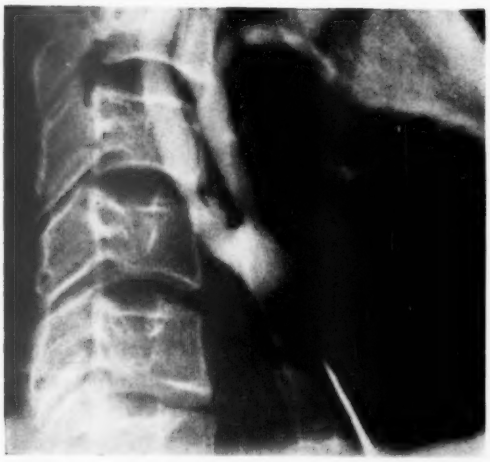

FIG. 2. A common carotid arteriogram demonstrating a partial obstruction of the internal carotid artery near its origin. It must be emphasized that considerably greater narrowing will be found at operation than is shown on the X-ray film

FIG. 3. The right carotid vessels, seven months after operation for the removal of a partial occlusion of the internal carotid artery, to show the smoothness of the intima and the absence of any intra-arterial obstruction

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OCULAR CHANGES IN GRAVES' DISEASE[1]

A Long-term Follow-up Study

By I. B. HALES and F. F. RUNDLE

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The ocular manifestations of Graves' disease are of great practical importance; in their severe degrees they cause conspicuous disfigurement. They may even threaten the integrity of the eyeball. Yet, as Chapman and Maloof (1955) have remarked, base-line observations on the natural course of the ophthalmopathy are lacking. The present report describes the eye signs found after the lapse of about 15 years in a group of patients originally studied by one of the authors. The previous records and measurements of 226 patients were available. They had suffered from one or other form of Graves' disease and hyperthyroidism. One hundred and four were traced and interviewed. Their ocular signs were measured again by the same techniques as had been used previously; and the results are here compared with the earlier findings.

In most published work on the ocular manifestations there is no clear definition of terms. Moreover, exophthalmos is said to be present, to improve, or to become worse, without measurements. Differences of local pathology and general aetiology have been presumed to be detectable from mere clinical inspection. For example, the clinician has been asked to distinguish infiltrative from non-infiltrative eye signs (Werner, Coelho, and Quimby, 1957), thyrotrophic from thyrotoxic exophthalmos (Mulvany, 1944), and malignant from non-malignant exophthalmos (Ruedemann, 1936). Furthermore, among patients described as having exophthalmic goitre, the attempt has rarely been made to exclude those merely showing lid retraction with hyperthyroidism. We have here described our findings in terms of certain ocular signs, namely, lid retraction, ophthalmoplegia, and exophthalmos. These signs may be adequately defined. They are indicative of damage to the extrinsic eye muscles and of changes in the bulk of retrobulbar and peribulbar contents of the orbit. The eyeball itself and the optic nerve remain normal. The present observations may be regarded as supplementing those published by Rundle (1945). It was then shown by serial monthly measurements that, in the course of one or two years near the onset of Graves' disease, protrusion and some degree of recession of the eyes may occur before a static phase is entered. In this static phase, despite patients' statements that the prominence of the eyes varied

[1] Received March 23, 1959.

greatly with their general mental and physical state, time of day, and other factors, actual measurements showed only variations within ± 2 mm. of the mean measurement, which is within the range of instrumental error. Many questions, however, were left unanswered by these relatively short-term observations. How stationary does exophthalmos remain over the years, and how much does it continue to affect the patient's appearance? Stepwise protrusion of the eye was found to occur in these earlier studies, and it was shown that the intervals between steps could be of many months' or years' duration, but the frequency of such intermittent activity in the ocular changes of Graves' disease was not established.

Methods

Definitions. The expression 'exophthalmic goitre' is used here to indicate the coexistence of one or more ocular signs and hyperthyroidism with its systemic effects. 'Ophthalmic forms of Graves' disease' are defined as those in which characteristic eye changes occur without goitre or hyperthyroidism. The ocular changes here considered include chiefly lid retraction, exophthalmos, and ophthalmoplegia. The expression *lid retraction* is used to signify retraction of the free border of the upper lid to the level of the limbus, or higher, in one or more of the standard directions of the gaze, horizontally forwards, fully upwards, or fully downwards. Normally the upper lid covers about 2 mm. or more of the cornea when the gaze is held steady in these standard directions. Lid retraction results from abnormal spasm of the levator palpebrae superioris (spastic type), or from overaction of this muscle associated with marked weakness of elevation of the eye (paralytic type), as described respectively by Pochin (1939) and Rundle (1953). The term *exophthalmos* is used to denote abnormal protrusion of the eyeball. Because of the wide range in prominence of the normal eye, the absolute diagnosis of exophthalmos, even using exophthalmometry, may be erroneous; but valid information as to protrusion or recession of the eye may certainly be obtained from comparison of serial exophthalmometer readings, as is done here. For the initial classification of patients, however, exophthalmos has been accepted as being present under the following conditions: (1) when the Hertel exophthalmometer reading was equal to, or greater than, 23 mm.; or (2) when one or other of the characteristic eye signs, lid retraction, ophthalmoplegia, or gross lid swelling, was associated with an exophthalmometer reading greater than the average found in normal control subjects ($16{\cdot}9 \pm 1{\cdot}8$ mm. by the present technique); or (3) when there was a clear history of recent bulging of the eyelids, with an exophthalmometer reading greater than 21 mm. All other patients have been classified as non-exophthalmic. Because of the tendency for the various eye changes to coexist, the probability of exophthalmos being present under conditions (2) and (3) is great. The term *ophthalmoplegia* is used to indicate limitation of elevation, abduction, adduction, or depression of the eyeball as demonstrated by vertometry

(Rundle and Wilson, 1942, 1944). The classification of such ophthalmoplegia into mild, moderate, or severe degrees is as previously described.

Patients Studied

Of the 104 patients traced, eight had had ophthalmic forms of Graves' disease, 59 had suffered from exophthalmic goitre, and 37 had been hyperthyroid, but had manifested no eye signs at their former measurement. The value of including patients lacking clinically detectable eye signs may be questioned. It is known, however (Rundle and Pochin, 1944), that they show changes in the orbital tissues qualitatively similar to those in exophthalmic goitre, and it was thought to be of interest to compare the long-term findings in this group with those of other clinical types. In all patients the follow-up measurements have been compared with the values found immediately before the long hiatus in assessments (hereafter referred to as 'the former measurements'). There was a hiatus of 13 years in nine patients, 14 years in 32, 15 years in 61, and 16 or more years in two. Three patients, originally manifesting only ocular changes, developed hyperthyroidism, requiring treatment by thyroidectomy, during the long hiatus. They have been classified as suffering from exophthalmic goitre, as have patients in whom the ocular changes, present before operation, became markedly worse in the first year or two afterwards. It is likely that the 104 patients comprise a representative sample of the 226 originally studied, except in so far as the lapse of about 15 years would tend to eliminate patients already elderly when seen previously.

The clinician is often faced with the problem: what is the outlook for the patient in whom ocular changes are still conspicuous some time after full control of the hyperthyroid component of Graves' disease? Included in the present series were 29 patients who, when formerly measured, were euthyroid but had gross ocular changes. Six had purely ophthalmic forms of Graves' disease. In the remaining 23 hyperthyroidism had been effectively controlled six months or more beforehand, yet unsightly eye signs remained. These 29 patients are hereafter referred to as the severely exophthalmic group, and the findings at their ultimate assessment are given separately (Table VIII). Four of them were judged to be hypothyroid at follow-up examination. Patients with severe eye changes in whom hyperthyroidism was still present at the time of the former measurements, or had only recently been controlled, were excluded from this group, as were the three patients in whom hyperthyroidism first developed during the hiatus.

Thyroidal status at former measurements. Sixty-four patients were considered to be euthyroid at the time of their former measurements (Group A). Apart from the three mentioned above who subsequently developed hyperthyroidism, the Group A patients give direct information concerning the effect of lapse of time only as regards the ocular manifestations. Nearly all had attended regularly for ocular measurements: where hyperthyroidism had existed, it had been effectively controlled at least six months before the former measurements. The

former measurements of the remaining 40 patients (Group B) were made while they were in hospital awaiting thyroidectomy for hyperthyroidism, and were made on this occasion only. In Group B the short-term effects of thyroidectomy on the ocular changes must be allowed for in assessing the remoter changes. Twenty-four Group B patients, however (60 per cent.), belonged to the class having hyperthyroidism without eye signs, and, except in one such patient to be described, no short-term effects were apparent. In 19 patients (the remaining 16 of Group B and the three of Group A who originally had 'ophthalmic Graves' disease' but developed hyperthyroidism during the hiatus)—that is, in about one-third of those with exophthalmic goitre—the factors of hyperthyroidism and its control may have influenced the comparison between the former measurements and those made at follow-up.

TABLE I

Sundry Data concerning Patients Traced

	Ophthalmic forms of Graves' disease (*8*)	*Exophthalmic goitre* (*59*)	*Hyperthyroidism without eye signs* (*37*)
Men	3	10	3
Women	5	49	34
Age at follow-up (years)			
Under 50	3	21	15
50–59	4	13	7
60–69	1	21	12
70+	0	4	3
Previous treatment			
Thyroidectomy	0	53	36
Antithyroid drugs alone	0	6	1
^{131}I therapy	0	0	1 (for recurrent hyperthyroidism)
Long-term thyroid therapy	1	6	1
Thyroidal state at follow-up			
Hyperthyroid	0	0	0
Euthyroid	8	50	35
Hypothyroid	0	9	2
Body weight at follow-up			
Increased	5	35	22
Stationary*	3	20	10
Decreased	0	4	5

* Classified as stationary if within $\pm$7 lb. of former weight.

Thyroidal status at follow-up, as detailed in Table I, was assessed solely on clinical criteria. It is likely that the true frequency of hypothyroidism somewhat exceeded that stated; because of the difficulty of diagnosing minor degrees of hypothyroidism on clinical grounds alone, borderline patients were classed as euthyroid. Where the patient's history during the hiatus suggested hypothyroidism, which appeared to be adequately corrected by current thyroid therapy, the patient was also classed as euthyroid; eight patients had been receiving thyroid extract for many years before reassessment. One had

ophthalmic Graves' disease, and myxoedema had supervened spontaneously. Many patients had been given thyroid extract irregularly for varying periods; no attempt has been made to allow for irregular thyroid therapy. The frequency of hypothyroidism was greater in patients formerly suffering from exophthalmic goitre than in those with hyperthyroidism only. Five patients of Group A and six of Group B had become hypothyroid. The frequency of delayed hypothyroidism was not significantly higher in the severely exophthalmic patients (four among 29) than in the other patients formerly manifesting ocular changes (five among 38).

TABLE II

Ophthalmic Forms of Graves' Disease

(*Eight Group A Patients*)

	At former measurement	*At follow-up*	
Lid retraction	6		1
Exophthalmos	7	Further protrusion	2
		Recession	3
		No change	2
Ophthalmoplegia	5	Disappeared	1
		Significantly less	3
		Unchanged	1

Techniques. With very few exceptions, the patients were examined by both authors. At the beginning of each follow-up we made a note independently, after brief inspection, as to whether or not the ocular changes were still apparent and, if so, whether they were slight or obvious. Thereafter a detailed history and examination were recorded. Methods of measuring the ocular changes were precisely as described previously (Rundle, 1957). At least four measurements of the prominence of the eyes and of each of the duction movements were made; these measurements were averaged to obtain the final reading for each. All readings for ocular prominence lying within ± 2 mm. of the former measurement have been classified as unchanged. Similarly, a difference in the range of any particular duction movement of 5° or less has been regarded as insignificant. In this follow-up the two eyes have generally behaved symmetrically. Thus it has been possible to pool the results for the two eyes of each patient. Where there was clear recession of one eye only, exophthalmos has been counted as decreasing in that patient, and similarly with the other ocular changes. No instance was encountered of an ocular change being clearly less on one side but increased on the other, when compared with the former measurements.

Results

Ophthalmic forms of Graves' disease (Table II). In these patients the general severity of the ocular changes had formerly been greater than in the remaining 96. They also showed relatively more change at follow-up. This may be accounted for, at least partly, by the limits imposed on our ability to detect changes by the techniques of measurement. Thus, a decrease of greater than

2 mm. in the exophthalmometer reading was required before recession of the eye was recorded. Clearly, where ocular protrusion was formerly very great, the same relative recession would be more readily detected than when it was slight. Certain patients in this group well illustrate salient findings of the whole follow-up:

Case 1. A male patient was formerly measured in April 1943. He was then aged 32, and presented typical lid retraction of spastic type on the right side, without exophthalmos or ophthalmoplegia. In the central direction of the gaze 0·5 mm. of sclera were exposed between the free border of the upper lid and the limbus, and in full depression the exposed scleral band widened to 3 mm. The characteristic skin crease was present at the level of the cutaneous insertion of the right levator palpebrae muscle (Pochin, 1939). On attempted light closure of the eyes the lid margins remained separated by 2 mm. on the right side.

When measured again in December 1957 he stated that his general health had remained good, and that he had never had any thyroid-affecting medication or thyroidectomy. Over the years he had gradually increased in weight by a total of 35 lb. Our first impression was that his eyes appeared normal. Clinically he appeared to be euthyroid. The right upper lid covered 2·5 mm. of cornea in the central direction, and 1 mm. of cornea in full depression, of the gaze. Ocular prominence and the range of eye movements were unchanged as compared with the former measurements. The skin crease in his right upper lid had disappeared, and the lid margins were apposed normally on light closure of the eyes.

Case 2. A male patient, now aged 51, had gained weight (from 147 lb. to 200 lb.) since his former measurements. He had never had any symptoms or detectable evidence of hyperthyroidism. In 1947 he gradually developed symptoms of hypothyroidism, and these became very severe until relieved by thyroid therapy in 1953. The ocular changes present formerly and at follow-up are summarized in Table III. Severe paralysis of elevation and hypophoric squint persisted on the right side, as did the lid retraction, which was of paralytic type; in fact, apart from some increase in ocular prominence and lid bulging, the ocular signs had remained static.

Case 3. A single woman was aged 39 when formerly measured in November 1943. She then showed well-marked unilateral lid retraction of spastic type on the right side, with bilateral exophthalmos and moderate lid protrusion, but no ophthalmoplegia. The Hertel exophthalmometer readings were R. 26·0 mm.; L. 24·25 mm.

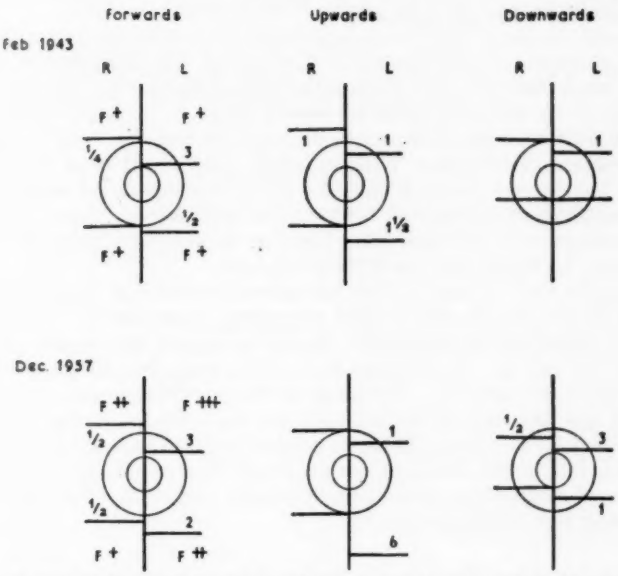
In December 1957 she stated that her general health had remained good; she had undergone no treatment, and appeared clinically to be euthyroid. In the interval she had gained weight (from 203 lb. to 241 lb.). Her lid retraction had disappeared completely. Eye movements remained full. Considerable bulging of the upper and lower lids had developed on both sides. The exophthalmometer readings had also increased to R. 28·5 mm.; L. 28·75 mm.

Case 4. A married woman, aged 34 when formerly examined in November 1941, then presented conspicuous bilateral lid retraction, with 1·5 mm. (right) and 2·5 mm. (left) of sclera exposed above the limbus in the central direction of the gaze. Diplopia and prominence of the eyes had been noticed during a recent (first) pregnancy, but there were no symptoms or signs of hyperthyroidism. Ocular movements were within normal limits except for abduction of the right eye, which was limited to 30°. This resulted in a disfiguring convergent squint, the anteroposterior axis of the right eyeball being turned in by 16°.

TABLE III

Case 2

I. *Lid Signs**



* The lid signs in right and left eyes are shown in the three standard directions of gaze, horizontally forwards, fully upwards, and fully downwards. The horizontal lines and numbers indicate the distance in mm. of the free margins of the upper and lower eyelids from the limbus.

Lid bulging is classified as mild (F+), moderate (F++), or considerable (F+++).

II. *Ocular Movements*

	Elevation R.	L.	*Other ductions*
February 1943	0°	20°	Within normal range both sides. Right hypophoria of 21°.
December 1957	3°	24°	Within normal range both sides. Right hypophoria of 20°.

III. *Exophthalmometer Readings*

	R.	L.
February 1943	21·5 mm.	21·75 mm.
December 1957	24·5 mm.	24·5 mm.

At follow-up in December 1957 she was still clinically euthyroid. She stated that her diplopia had lessened greatly within a few months of her previous attendance, and had disappeared completely after one or two years. Examination showed that she had lost her lid retraction and squint completely, though some limitation of abduction of the right eye persisted:

	Horizontal ductions			
	R. eye		*L. eye*	
	out	*in*	*in*	*out*
November 1941	30°	45°	53°	42°
December 1957	35½°	45°	46°	45°

The prominence of the eyes had decreased slightly (by 1·5 mm. on the right and 2·75 mm. on the left) in spite of a gain of 21 lb. in weight. Thus a rather modest improvement in the power of the right external rectus enabled this patient to regain conjugate vision. This, and the disappearance of lid retraction, resulted in her recovering a normal appearance.

Case 5. A male patient was aged 32 when he first attended in September 1941. He could then not even elevate the eyes to the horizontal plane. During the ensuing 19 months elevation improved slightly; with his head fixed in a rest, and Reid's base line horizontal, he could eventually hold his eyes in the central direction of the gaze. With an effort they could even be temporarily elevated a few degrees above it, but the effort was associated with intense discomfort and blepharospasm, and could not be maintained. Associated with the ophthalmoplegia were bilateral lid retraction of paralytic type, exophthalmos (R. 24·0 mm; L. 26·75 mm.), and lid protrusion.

In December 1957 he stated that his general health had remained good, and that he had not sought any special treatment since last attending. He still appeared clinically to be euthyroid. His body-weight had remained steady at approximately 147 lb. Re-examination of the eyes showed some recovery of elevation (right 15°; left 14°). His paralytic lid retraction was no longer present. Fullness of the lids had decreased, and the exophthalmometer readings were R. 22·25 mm.; L. 24·0 mm. Thus, in spite of useful recovery of elevation, the range of this movement was still less than half of the normal. Some disability resulted, as shown by persistent compensatory torticollis in extension. Paralytic lid retraction had disappeared.

Exophthalmic goitre. The results in this group are summarized in Table IV. Lid retraction had disappeared in 25 of 44 patients. The lid retraction had been spastic in type in 25, paralytic in 13, and not classified or indeterminate in six patients. Two-thirds of those with spastic lid retraction lost it, as compared with approximately one-third of those with paralytic retraction. There was a strong tendency for paralytic retraction to disappear when paralysis of elevation improved, but in five patients such retraction disappeared when ophthalmoplegia persisted unchanged. Improvement in lid retraction is of immense cosmetic inportance, because it creates the illusion that the eyes have receded. It is clear from Tables II and IV, and it is fortunate, that the lid retraction of Graves' disease is the sign most likely to improve with time. It is known that thyroidectomy, or effective control of hyperthyroidism by other means, quickly results in some improvement in lid retraction (Bothman, 1934; Eden and Trotter, 1942; Soley, 1942; Rundle, 1945) but, because of the absence of Group B patients from Table II and the relatively small number of Group B patients included in Table IV, control of hyperthyroidism was not an important factor in the improvement here noted.

A related sign is failure of the lid margins to meet on attempted light closure of the eye (hereafter termed 'lid separation'). When lid separation is present, the eye often remains open during sleep. Conjunctivitis and effects of exposure may result. Especially if associated with marked exophthalmos and overcrowding of the orbits, lid separation involves a real threat to vision. It is remarkable how rarely lid separation persisted at follow-up (in only three of

17 cases), considering that proptosis generally remained unchanged or increased. The general decrease in lid retraction seems scarcely to provide a sufficient explanation for the eyelids becoming apposable. It is possible that in long-standing exophthalmos compensatory stretching of the eyelids gradually occurs, facilitating apposition of their margins on light closure. Whatever the explanation, the restoration of apposition greatly reduces the risk of severe intercurrent exposure and infective complications.

TABLE IV

Exophthalmic Goitre

(43 Group A and 16 Group B Patients)

	At former measurement		*At follow-up*	
Lid retraction	44	. . . . .	19	
Exophthalmos	58	Further protrusion	15	2·25 to 4 mm. 12; 4·25 mm. or more 3
		Recession of 2·25 to 4 mm.	2	
		No change	41	
Ophthalmoplegia	24	. . . . .	30	Newly developed: mild 5, moderate 1, severe 0
				Old: unchanged 12, significantly less 7, significantly worse 5

Regarding the proptosis in patients with exophthalmic goitre, in 70 per cent. of those followed-up the exophthalmometer reading lay within ± 2 mm. of the former measurements. In only three patients (5 per cent.) was there marked further protrusion of the eyes (in one patient by 6·25 mm. (R.) and 5·75 mm. (L.)). The conclusion is thus inescapable that in most patients exophthalmos had already reached a maximum and static phase by the time they were referred to us.

Ophthalmoplegia in about one-half of the patients persisted unchanged, in about one-quarter it was worse, and in one-quarter it was improved. Six of 29 patients previously unaffected showed some limitation of elevation at follow-up examination. This new development of ophthalmoplegia may be partly due to advancing years, since the range of eye movements is demonstrably less in elderly subjects (Rundle and Wilson, 1942). The most disabling consequence of ophthalmoplegia is squint, developing when asymmetry in the range of conjugate ductions is marked. Table V gives details of the eight patients formerly affected by squint. At follow-up the squint had disappeared in four, although asymmetry of about 10° in the relevant conjugate movements persisted in three of the four. In the four patients who had not lost their squint the persisting asymmetry was greater than this. Evidently the faculty of fusion may compensate for asymmetry of the order of 10° or less.

Hyperthyroidism without ocular changes. Of these patients (Table VI) approximately one-fifth had developed a relatively minor increase in ocular prominence, and limitation of elevation of 5° to 8°; no disability resulted. In the remaining patients, with one exception, ocular changes were not found. The exceptional

patient, a married woman aged 52 when measured in June 1942, then presented no detectable ocular changes. Shortly afterwards she underwent subtotal thyroidectomy. During the following year her eyes became prominent, and eventually were very uncomfortable and conspicuous. The skin over the front of the shins also became swollen and leathery. At follow-up in December 1957

TABLE V

Follow-up of Paralytic Squint

Class and number of patient	*Former squint*	*Affected conjugate duction: maximum ranges (degrees)*				*Asymmetry of eye movement (degrees)*		*Squint at follow-up*
		Elevation						
		Formerly		*At follow-up*		*Formerly*	*At follow-up*	
		R.	*L.*	*R.*	*L.*			
Exophthalmic goitre:								
1.	Hypophoric (R.) 12½°	15	27½	7	18	12½	11	Hypophoric (R.) 6°
2.	Hypophoric (R.) 35°	16½	26½	20	29	10	9	Nil
3.	Hypophoric (R.) 17°	17	35	22	31	18	9	Nil
4.	Hyperphoric (R.) 21°	38	33	36	36	5	0	Nil
Ophthalmic forms of Graves' disease:								
5.	Hypophoric (R.) 21°	0	20	3	24	20	21	Hypophoric (R.) 12°
6.	Hypophoric (L.) 25°	21	0	21	7	21	14	Hypophoric (L.) 12°
7.	Convergent (L.) 15°	*To left* 42	27	40	27	15	13	Convergent (L.) 18°
8.	Convergent (R.) 16°	*To right* 31	46	35½	46	15	10½	Nil

TABLE VI

Hyperthyroidism Without Eye Signs

(13 Group A and 24 Group B Patients)

		At follow-up
Lid retraction	Present in	0
Ocular prominence	Increased in	7 (by 2·25 mm. to 4 mm. in 6; by 4·25 mm. or more in 1)
	Decreased in	0
	Unchanged in	30
Ophthalmoplegia	Mild or moderate in	6
	Severe in	1

the ocular changes were still gross. The right eye had protruded by 5·25 mm., and the left eye by 5·5 mm. The lids were considerably bulged. Chemosis and epiphora were present. The range of elevation of both eyes was severely limited; other duction movements were full. Typical pretibial myxoedema was present in both legs. It is noteworthy that in this patient the former measurements failed to detect any abnormal eye signs. Nearly all patients with

so-called post-operative exophthalmos have manifested some ocular changes beforehand; these changes merely increase greatly afterwards.

Patients with severe exophthalmos. In about one-half of these patients the ocular changes at follow-up appeared to be slight or absent (Table VII). This cosmetic result depended almost entirely on improvement in lid retraction; recovery from squint also contributed. As already mentioned, control of the hyperthyroid component of Graves' disease results in some decrease in lid retraction, but such control was not a factor in any of these patients. Their lid retraction evidently decreased more gradually. Both spastic and paralytic

TABLE VII

The Severely Exophthalmic Group

(29 Group A Patients)

	At former measurement	*At follow-up*
Lid retraction . . .	24	12
Exophthalmos and bulging of lids	29	25 (recession of 4·25 mm. or more in 1)
Ophthalmoplegia . . .	16	16
Clinical impression:		
Ophthalmopathy obvious .	29	15
slight .	0	9
absent .	0	5

types of retraction improved or disappeared with time. In individual patients in whom retraction persisted, it retained its original characteristics, though usually at a reduced level. For example, in two patients (described in detail by Rundle, 1953) spastic lid retraction was markedly less at follow-up, but on close examination indrawing of the skin of the upper lid at the levator palpebrae insertion still occurred in depression of the gaze; and the resulting skin crease preserved its characteristic eyebrow shape. Slight hitching up of the lid margin was also evident.

Discussion

The above results may be discussed briefly in reference to the ocular manifestations themselves, the inference we may draw concerning the orbital tissue changes, and the light these throw on the flow and ebb of the general hormonal factors in Graves' disease.

Among the patients here described, as originally studied and then followed-up after 15 years or more, marked ocular changes occurred in less than one-third. Because of the special interest of one of the authors in the eye signs, it is probable that this proportion considerably exceeds the general frequency of marked ocular changes. It is likely that exophthalmos in Graves' disease is usually mild or moderate in extent. It is also clear that exophthalmos, if it is absent when hyperthyroidism is controlled, very rarely develops subsequently.

It seems that exophthalmos and related signs generally reach their peak relatively early in the course of Graves' disease. In fact, our data indicate that

exophthalmos had usually reached its maximum extent by the time the patient was referred for treatment of associated hyperthyroidism. The dynamic phase of the ocular changes may be characterized by protrusion and recession of the eye (Rundle, 1945), but it is clear from the present long-term study that significant degrees of recession of the eye occur only exceptionally. If there is recession, it follows hard on the peak of protrusion. In most patients exophthalmos becomes static near its maximum. In eyes apparently static after a year or two, measurements of ocular prominence 15 years later generally showed little or no change. Delayed recession or delayed further protrusion is exceptional. Nevertheless, in about one-half of the patients who were at first left with severe ocular changes after control of their hyperthyroidism, eye signs had become slight or absent to ordinary scrutiny 15 years later. This cosmetic improvement resulted from decrease in lid retraction, and from recovery of muscle power sufficient to overcome squint in a proportion of patients.

The orbit is a cone-shaped bony socket, closed posteriorly, and Pochin (1947) has likened the eyeball to a tambour accurately reflecting changes in the bulk of the orbital tissues. It is known that in wasting the eye tends to be sunken, and in obesity to be protruberant; but the corresponding changes of bulk in the orbital tissues may be of minor degree compared with those in Graves' disease. Thus when the trends of general nutrition and of Graves' ophthalmopathy are contrary, the effect of the latter often predominates. It is likely that in classical Graves' disease conflicting influences play on the orbital tissues, in sum reducing or increasing their bulk. Classically the orbital tissues enlarge, while the body wastes generally. Inversely, when the ocular manifestations are improving, the eye may recede steadily, indicating shrinkage of orbital tissues, in spite of a gain in body weight (Rundle, 1945). The majority of patients here studied had gained weight (Table I). It is likely that this gain contributed in some measure to the maintenance or increase of protrusion of the eyes.

That damage to muscle function is more readily restored than change in bulk of the orbital tissues is suggested by the frequent disappearance or lessening of lid retraction. With the muscles governing eye movements the position is complicated by the effects of contraction of the antagonists, and of fibrosis in and around the muscles. Nevertheless, spontaneous recovery from paralytic squint occurred in four of eight patients so affected. In contrast, increase in tissue bulk produced during the acute stage of the hormonal upset is irreversible in a high proportion of patients. The biochemical changes originally responsible for the enlargement may give place secondarily to other changes which endure indefinitely. Pochin's experiments (1949) may have some relevance. He demonstrated that fat tends to infiltrate a cavity artificially produced in the rabbit's subcutaneous tissue. That the tissue changes maintaining proptosis and lid protrusion are secondary and non-specific in character is suggested by their persisting unchanged in spite of disappearance of lid retraction and improvement in ophthalmoplegia.

The flow and ebb of hormonal influences in Graves' disease, and their varied effects, may be indicated appropriately by reference to one of the present

patients, a woman now aged 62. In 1940 she first came under observation with classical Graves' disease; a bilateral thyroidectomy was done. Two further recurrences of thyrotoxicosis required thyroidectomy, first in February 1941, and then in May 1942. During these years she was thin, highly apprehensive, and showed steadily increasing exophthalmos. Thus in February 1941 her exophthalmometer readings were R. 22·5 mm.; L. 21·5 mm. By August 1942 they were R. 28·0 mm.; L. 27·0 mm. Between November 1942 and June 1943 extensive pretibial myxoedema developed in both legs, and was confirmed by biopsy. At her former measurements (January 1944) there was marked lid retraction, but no ophthalmoplegia. The Hertel readings were R. 28·75 mm.; L. 27·25 mm. In December 1957 lid retraction was no longer present. Eye movements were still full. The Hertel readings were R. 29·5 mm.; L. 29·25 mm. The pretibial myxoedema had completely disappeared. Her body weight was unchanged. She appeared euthyroid clinically, though certain symptoms suggested hypothyroidism.

It is desired to acknowledge help received in this follow-up from Professor Russell Fraser and his staff. We are also grateful to the Research Committee of the Westminster Hospital School of Medicine for arranging the facilities to see these patients. The work was aided by a grant from the Medical Research Council, and was done during the tenure by one of the authors (I. B. H.) of a Leverhulme Research Scholarship of the Royal College of Physicans.

Summary

1. A group of 104 patients previously suffering from one or other form of Graves' disease and hyperthyroidism was traced after the lapse of about 15 years. The former measurements of their eye signs were compared with those made at follow-up.

2. Exophthalmometry showed that in 75 patients the prominence of the eyes was unchanged; in 24 ocular prominence had increased by more than 2 mm.; in five the eyes had receded by more than 2 mm. One patient, in whom eye signs were formerly lacking, had developed severe exophthalmos and ophthalmoplegia. In three others former exophthalmos had progressed considerably.

3. Ophthalmoplegia similarly remained unchanged in approximately two-thirds of the patients. Six others, not formerly affected, had demonstrable limitation of eye movements at follow-up. Paralytic squint had formerly been present in eight patients. In four of them spontaneous recovery of muscle function was such that squint was no longer present at follow-up.

4. Lid retraction had disappeared in 60 per cent. of the patients so affected, and in others it had generally decreased in extent. The general appearance of the patients had improved greatly in consequence, though in about 50 per cent. of those who formerly had conspicuous eye changes ophthalmopathy was still obvious at follow-up.

5. Separation of the lids on attempted light closure of the eyes, commonly persisting during sleep, had disappeared in 14 out of 17 patients so affected.

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GOUT, FAMILIAL HYPERURICAEMIA, AND RENAL DISEASE[1]

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With Plate 10

PRIMARY gout is often a familial disease, and is characteristically accompanied by increased serum uric acid. Non-gouty relatives of gouty subjects may also show an increase in serum uric acid, suggesting that incomplete manifestations of the gouty tendency occur. Renal complications of gout are common, particularly in the later stages. The present paper records the close association of hyperuricaemia and renal disease in a young family, only one member of which has gouty arthritis, and explores the possibility that hyperuricaemia may itself lead to renal damage.

Methods

All subjects except one (Na.) were examined personally at hospital or at their homes on several occasions. Blood-pressures were measured with the patient seated, and two readings taken at an interval of between five and ten minutes. All biochemical investigations were performed in the same laboratory. Early morning specimens of urine were tested for albumin by heating and by salicylsulphonic acid. Fresh specimens of urine were centrifuged, and the deposit examined microscopically. Samples of venous blood were taken at least three hours after a meal. Serum uric acid was determined by a modification (King and Wootton, 1956) of the uricase method described by Feichtmeir and Wrenn (1955). The upper limit of normal has been accepted as 6·0 mg. per 100 ml. for male and 5·0 mg. per 100 ml. for female subjects. The normal range for blood urea is 12 to 47 mg. per 100 ml. (King and Wootton, 1956). Each value shown in the Table is a mean of at least three separate observations.

Clinical Account of the Family

The propositus (F.) was a well-looking 19-year-old builders' labourer. At the age of 14 years, after trauma to the left foot, he experienced classical podagra, which lasted four days; since then similar attacks of acute arthritis have affected the right great toe, the ankles, left knee, wrists, hands, and fingers.

[1] Received April 11, 1959.

He was discharged from the Army at the age of 18 after two attacks of arthritis which had affected the hands and wrists. A recurrence in the right wrist led to his admission to another hospital. Hypertension and albuminuria were found, and he was transferred to the care of Professor J. McMichael at this hospital for further investigation and treatment. Between attacks of arthritis he led an active life, doing heavy manual work, with rock climbing and football in his spare time. He had had no previous illnesses, and there was no family history of joint disease. His acute arthritis settled without specific therapy. Bony enlargement of the metatarsophalangeal joints of the first and second toes of both feet, and a small tophus attached to the left elbow, were the only residual changes.

The blood-pressure varied between 200 and 160 systolic, and between 140 and 100 diastolic. The fundi showed slight arterial narrowing. The erythrocyte sedimentation rate was initially 18 mm., and later 8 mm., in one hour. The haemoglobin concentration was 13·4 g. per 100 ml., and the white-cell count 10,000 per cu. mm., with a normal differential count. The blood urea was 106 mg. per 100 ml., and the serum uric acid was 16·0 mg. per 100 ml. No 'lupus erythematosus cells' were found in the peripheral blood on two attempts, and the differential sheep-cell agglutination test for rheumatoid arthritis was negative. Albuminuria was present, and estimations in three 24-hour specimens of urine showed daily excretions of 1·6 g., 0·8 g., and 0·5 g., while corresponding urinary urate outputs were 0·6 g., 0·5 g., and 0·4 g. Abnormal aminoaciduria was not present. The urine was concentrated to a specific gravity of 1,014 after 15 hours' water deprivation, and was diluted to 1,006 after a water load of 1,500 ml. An electrocardiogram and a radiograph of the chest both showed evidence of left ventricular enlargement. Radiographs of the feet (Plate 10, Fig. 2) showed cystic defects of bone at the first and second metatarsophalangeal joints. The area of the renal shadows shown in radiographs of the abdomen was markedly diminished, being estimated (Hodson, 1959) as 65 to 70 per cent. of that expected for the patient's age and build. An excretory pyelogram showed that the dye was not concentrated by either kidney. Biopsy of these small kidneys was unsuccessful. There was no clinical or biochemical evidence of other causes of juvenile hypertension, such as phaeochromocytoma or coarctation of the aorta. Cushing's disease was excluded clinically, and there were no features of Marfan's syndrome (Loughridge, 1959) or hereditary diseases which might affect the kidney, other than gout.

The patient's history, together with a markedly increased serum uric acid and the characteristic radiological changes, were together considered to be diagnostic of gout. The hypertension, uraemia, small kidneys, and failure of dye concentration, were characteristic of fairly advanced renal failure. The question arose whether the gout was primary, and coincidently associated with renal disease, or secondary gout which had followed urate retention caused by the renal disease. The serum uric acid level seemed too high for the degree of urea retention, since in chronic uraemia of this degree serum uric acid levels of 2 to 7 mg. per 100 ml. are more usual. Further evidence on this point was

pursued by investigating the patient's relatives: if primary gout were the condition, some of the relatives might show increased serum uric acid.

The pedigree of this family, and some individual features, are shown in Fig. 1. It is notable that both parents and all surviving sibs had hyperuricaemia. Further features were as follows:

J. (the father) was well, and had never had gout. Neither of his parents, nor any of his 11 siblings, suffered from joint disease.

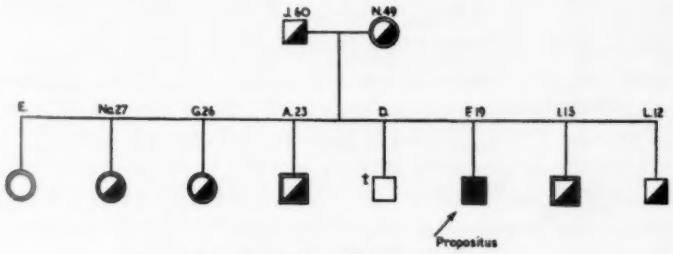
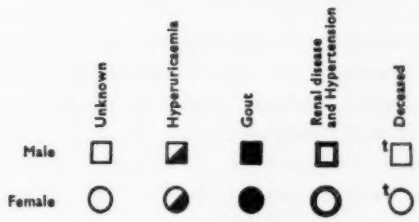


FIG. 1. Pedigree of the family.



N. (the mother) had never had gout, and there was no family history of gout; but she had developed toxaemia, with hypertension and albuminuria, in the last two of her eight pregnancies.

E. (sister) died in 1944, aged 14, at another hospital. She had developed hypertension (200 mm. Hg systolic, diastolic unrecorded) with papilloedema, albuminuria, a blood urea of 160 mg. per 100 ml., and anaemia. The serum uric acid was not estimated. At autopsy the kidneys were small, contracted, and granular. Formalin fixation made identification of urates impossible; but on the section available Professor C. V. Harrison commented that 'there are no large spaces which might have represented urate deposits. The picture as a whole suggests chronic pyelonephritis, particularly in the presence of capsular glomerular adhesions. There is also evidence suggestive of gout in the form of basophilic casts in second convoluted tubules. These casts contrast with the majority which are eosinophilic.'

Na. (sister) had had one successful pregnancy complicated by pre-eclamptic toxaemia with hypertension, fluid retention, and albuminuria. There had been two previous miscarriages. She was again pregnant at the time of this study, and again showed signs of toxaemia. Her six-year-old son was normotensive, and his serum uric acid was 3·5 mg. per 100 ml.

G. (sister) developed pre-eclamptic toxaemia with hypertension and albuminuria during her only pregnancy. Estimations on her infant have not been performed.

D. (brother) died of pneumonia at six months.

Subject	*Age (years)*	*Relationship*	*Blood-pressure (mm.Hg.)*	*Blood-urea (mg./100 ml.)*	*Serum uric acid (mg./100 ml.)*	*Renal disease and hypertension*
J.	60	Father	145/80	32	9·4	—
N.	49	Mother	250/130	51	6·0	+++
E.	Died aged 14	Sister	200/..	160	..	+++*
Na.	27	Sister	180/120	56	11·7	++
G.	26	Sister	150/100	48	6·5	++
A.	23	Brother	120/70	53	7·7	+
D.	Died aged $\frac{6}{12}$	Brother	..	..	..	..
F.	19	Propositus	200/100	106	16·0	+++
I.	15	Brother	115/90	50	12·7	+
L.	12	Brother	120/85	38	7·0	—

* Renal disease cause of death.

I. (brother) was perfectly well. He had experienced one episode of pain in the great toe after local trauma; this might have been gout, but there were no residual clinical or radiological changes. (See *Note* on page 134.)

L. and A. (brothers) were clinically normal.

Discussion

This family study thus provided convincing evidence that our patient had primary gout. It seems likely that both parents carried the hyperuricaemic trait, and had passed it with 100 per cent. penetrance to their children. Seven of the nine first-degree relatives surviving beyond infancy had some evidence of renal disease; the father (J.) and youngest brother (L.) were significant exceptions. This family thus provided clear evidence that hyperuricaemia could occur without renal disease, but renal disease did not occur without hyperuricaemia. Hyperuricaemia is the primary defect, and renal disease the complication. The term 'hyperuricaemic nephropathy' seems justifiable. The disorder occurs in the absence of clinical gout, and it may come to notice as chronic nephritis, as renal hypertension, and possibly as pre-eclampsia, or even as mild urea retention.

Subjects with primary gout, and a high proportion of their symptomless relatives, show increased serum uric acid, the co-called 'essential hyperuricaemia' (Smyth, Cotterman, and Freyberg, 1948; Stecher, Hersh, and Solomon, 1949). In primary gout and essential hyperuricaemia there is an increased synthesis of urates, either by an acceleration of normal nucleic-acid-purine metabolism or by a direct synthesis from simple nitrogen- and carbon-containing compounds (Furst, Roll, and Brown, 1950; Benedict, Roche, Yü, Bien, Gutman,

and Stetten, 1952; Stetten, 1954; Wyngaarden, 1957). Garrod's (1876) hypothesis, that gout is the result of relative failure of the kidney to excrete uric acid, has not been proved correct by later work (review by Gutman and Yü, 1957). Nevertheless there is abundant clinical evidence that gout is often complicated by renal disease. McQueen (1951) studied the clinical course of 60 unselected patients with gout, and showed that 36 (60 per cent.) developed albuminuria, haematuria, pyelonephritis, or nitrogen retention. In another clinical study Sougin-Mibashan (1954) observed that 52 (40 per cent.) of 130 gouty patients showed similar evidence of renal malfunction. Wyngaarden (1958) stated that 30 to 50 per cent. of patients with gout die of renal disease or its complications. Autopsy findings are in agreement. Thus Garrod (1876), Schnitker and Richter (1936), Brown and Mallory (1950), Modern and Meister (1952), Fineberg and Altschul (1956), and Sokoloff (1957) have reported post-mortem evidence of renal damage in from 80 per cent. to 100 per cent. of patients with gout. They emphasized the variety of renal lesions which may occur, not only related to urate deposition, such as uric acid stones, tubular block by urates with flattening and necrosis of tubular epithelium, interstitial urate deposits, tophi in the renal pyramids, and urate infarcts, but also less obviously related lesions, such as interstitial nephritis, pyelonephritis, and nephrosclerosis. The primary renal lesions are often complicated by infection or the effects of hypertension.

Hyperuricaemia following blood diseases (chiefly polycythaemia, myelosclerosis, haemolytic disorders, and certain forms of leukaemia) is associated with an increased degradation of cell nuclei (Wyngaarden, 1957) or with a specific megakaryocytosis of the bone-marrow (Hickling, 1958), and may lead to secondary gout. The metabolic pathway leading to the over-production of urates in these conditions is normal (Yü, Weissman, Sharney, Kupfer, and Gutman, 1956). Gout is rare in acute leukaemia, possibly because patients die before it has time to develop, although three cases have been reported in children (von Schopf, 1930; Vining and Thompson, 1934; Franck, 1944). Nevertheless renal damage does occur in association with this cause of hyperuricaemia, for we have observed tubular blockage by urates, causing renal failure, in a child aged seven with acute leukaemia. Similar cases, usually following irradiation or treatment with cytotoxic agents, have been reported (Bedrna and Polcack, 1929; Lambie, 1940; Merrill, 1940; Lear and Oppenheimer, 1950; Kravitz, Diamond, and Craver, 1951; Weisberger and Persky, 1953; Greenbaum and Hope-Stone, 1959). Moreover, careful histological examination at autopsy frequently reveals urate crystals in the tubular wall or lumen (Büchner, 1956) in untreated acute leukaemia. In chronic myeloproliferative disorders hyperuricaemia is frequent; clinical gout complicates polycythaemia, for example, in about 5 per cent. of cases. In our experience this form of gout is also associated with renal damage.

A 52-year-old male porter, diagnosed in 1947 as having polycythaemia vera, first developed acute gouty arthritis after treatment with radioactive phosphorus in 1948. Tophi and albuminuria were noted in 1949. A renal biopsy

in 1956 showed changes compatible with pyelonephritis, but urate crystals were not seen, although specifically looked for. The albuminuria persists at the time of writing, and the blood urea is 78 mg. per 100 ml.

We have found no published evidence as to the prevalence of renal disease in patients with primary or secondary hyperuricaemia without gout, or the prevalence of renal disease in the relatives of gouty patients, apart from the study of Hauge and Harvald (1955), who found a frequency of renal calculi in relatives of gouty subjects which was five times that found in relatives of non-gouty control subjects. Such a case was reported by Fineberg and Altschul (1956): a 57-year-old man, whose father had had gout, was found to have pain from urate gravel. The relationship of renal disease to hyperuricaemia may be illustrated by recent patients.

A man aged 39 came to this hospital with a six years' history of recurrent monthly episodes of renal colic, haematuria, and the passage of stone and gravel. His blood-pressure and renal function were normal; excretory and retrograde pyelograms were normal, but the serum uric acid was persistently increased at 7·0 mg. per 100 ml. There was no family history of gout or renal disease.

A 57-year-old man, who was admitted for investigation of hypertension (blood-pressure 190/140), gave a history of renal colic, but had no symptoms suggesting infection of the renal tract. There was no family history of gout or renal disease and, though his blood urea was 32 mg. per 100 ml., his serum uric acid was 7·8 mg. per 100 ml. Urate crystals were seen in abundance in the spun urine deposit, but no calculi were passed during the period of observation.

A man aged 38 came to the Canadian Red Cross Memorial Hospital, with a 'lump as big as a cherry' on the dorsum of the left fifth metacarpophalangeal joint. This lump was aspirated, and urates demonstrated. There was no family history of renal disease or gout. Blood-urea estimations ranged between 158 mg. and 176 mg. per 100 ml., and the serum uric acid was 10·4 mg. per 100 ml. The patient was hypertensive (blood-pressure 230/130), renal function was poor, urinary infection was present, and a diagnosis of 'chronic pyelonephritis' was made on renal biopsy. Later he developed three mild attacks of gout in the knee and foot.

A review of the last 61 patients with gout admitted to this hospital during the past 10 years showed four who gave histories of renal colic and urolithiasis which had occurred before their first attack of gout, and all four patients were hypertensive at that time. Garrod (1876) was aware that urolithiasis could precede gout by many years, and described a patient who suffered his first attack of gouty arthritis at the age of 90, having had a lithotomy performed 78 years previously. In summary, there is evidence that all naturally occurring causes of hyperuricaemia can be followed by renal disease. Renal involvement in cases of primary gout, or in the members of the family under discussion, is thus not due to a common inheritance of both the hyperuricaemic trait and a separate trait for renal disease.

Hyperuricaemia accompanies such acute renal diseases as acute glomeru-

lonephritis or pre-eclamptic toxaemia, and returns to normal with renal function. Hyperuricaemia may also occur in association with the nitrogen retention of chronic renal disorders, but is rarely severe, since in chronic renal disease diminished glomerular clearance of urate is 'compensated' by decreased tubular reabsorption of filtered urate. The suggestion of Garrod (1876) that, in certain stages of renal disease, the retention of nitrogen and of urates may be independent of each other, has been well demonstrated by Chesley (1950) in patients with pre-eclampsia. It is doubtful whether gout secondary to chronic renal disease ever occurs (Gutman, 1953), for severe degrees of renal failure are usually necessary to produce a significant hyperuricaemia, and patients rarely live long enough to develop gout. Animal experiments are of limited relevance, for, except in anthropoid apes, the metabolism of uric acid is different from that occurring in man. But acute experiments, involving large intravenous infusions of urate into dogs, cats, goats, and rabbits (Folin, Berglund, and Derick, 1924; Dunn and Polson, 1926; Smith and Lee, 1957), showed an immediate and damaging effect confined to the kidneys, which within two hours of the infusion became pale, swollen, and oedematous. Nitrogen retention occurred with oliguria, lasting several days. Attempts at producing chronic hyperuricaemia in rabbits have been made by Dunn and Polson (1926), who used smaller urate infusions given for a period of 19 days. The blood-urea level was observed to rise, but complete recovery followed suspension of the daily infusions. The renal lesion in both groups of experiments was similar: localized tubular damage, the degree of which depended on the dose and duration of the hyperuricaemia. Folin, Berglund, and Derick (1924) gave infusions of urate, 20 mg. per kg., to human volunteers, and showed that the blood urea increased. Berliner, Hilton, Yü, and Kennedy (1950) repeated this experiment but varied the load, and found that the serum-urate level usually remained elevated for a period of two days. One subject, whose serum urate reached 26 mg. per 100 ml. after an infusion of 100 mg. per kg., showed renal insufficiency with oliguria for 36 hours, and increased blood urea for 14 days, before complete clinical and biochemical recovery. These experiments were of relatively short duration compared with the clinical states under discussion, but suggest that high serum-urate concentration can be nephrotoxic.

Familial hyperuricaemia should therefore be considered as a possible cause of renal hypertension, particularly in young people, even in the absence of gout. These considerations have ceased to be of solely academic significance, since the uricosuric agent probenecid has given us an effective agent for reducing hyperuricaemia which is safe and well tolerated over long periods. Toxic effects have been uncommon, and an increased excretion of urates has been followed by the gradual dispersal of visible tophi. Thus not only the serum urate, but also the extravascular urate can be reduced. In our experience, which agrees with that of Phillips (1955) and Brøchner-Mortensen (1958), it is always worth giving probenecid to patients with gout and renal disease, and we have observed significant improvement, not only in the circulating serum-urate level, but also in the blood-urea concentration and renal function tests. Six months' probenecid

therapy to the propositus of this study has been associated with a reduction of the serum uric acid level from 16·0 mg. to 7·8 mg. per 100 ml., and a fall of the blood-urea level from 106 mg. to 81 mg. per 100 ml. Sirota, Yü, and Gutman (1952) pointed out that on theoretical grounds there is still, in renal disease, considerable tubular reabsorption of urate from the glomerular filtrate. This absorption may be diminished by probenecid. Thus there is good reason to give this drug in hyperuricaemic nephropathy, with or without gout, and to expect improvement in renal function, especially in the early phase of damage, and when renal function is impaired by interstitial deposits of urates. It might be thought that probenecid would increase urate deposition in collecting passages, but Talbott (1958) and Bernstein, Bronsky, and Dubin (1958) have reported its beneficial administration to patients with uric acid urolithiasis.

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Summary

A youth aged 19 presented severe renal hypertension, and was found to have mild gout. His seven surviving first-degree relatives all had hyperuricaemia, and all but two of them showed evidence of renal disease. One sister died at the age of 14 from hypertensive renal failure. His mother and his two sisters had hypertension and developed pre-eclamptic toxaemia. The remaining two affected brothers (aged 23 years and 15 years) had albuminuria and a raised blood-urea level.

In this family hyperuricaemia appeared to have caused the renal disease. The concept of hyperuricaemic nephropathy is examined. Evidence supporting the hypothesis that a raised serum-urate concentration is damaging to the kidney has been assembled from studies of other pathological and experimental causes of hyperuricaemia.

Familial hyperuricaemia, a treatable condition, should be considered as one of the causes of renal hypertension, especially in young people.

Note. The younger brother of the propositus, I., has now (December 1959) developed radiological evidence of urate deposits in both first metatarsophalangeal joints, and his blood-pressure has risen to 158/110. There has been no further evidence of gouty arthritis.

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FIG. 2. Bone defects at the first and second metatarso-phalangeal joints of the propositus

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AMYLOID DISEASE OF THE KIDNEY AND RENAL VEIN THROMBOSIS[1]

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With Plates 11 to 13

About 80 years ago W. Howship Dickinson, physician to St. George's Hospital, London, wrote: 'The knowledge that clot sometimes forms during life in the veins of the kidney is nothing new in pathology, though from its comparative infrequency it occasionally drops out of notice, to reappear like an old fashion restored with the freshness of novelty.' Renal venous thrombosis in the adult is seldom a primary event. More often it occurs as a serious complication of cardiovascular, neoplastic, or intrinsic renal disease. Of the last-named group amyloidosis is an important example, and its significant relationship with renal venous thrombosis was noted in 1885 by Dickinson. In infants primary thrombosis of the renal veins, occurring in states of severe dehydration, commonly results in fatal, massive, haemorrhagic infarction of the kidneys, resembling that produced by venous ligation in the experimental animal (Harrington, 1921). In the adult, however, the functional and anatomical result of renal venous thrombosis is more varied, depending apparently not only on the speed of the thrombotic process, but also on its site within the renal venous system.

Previously Reported Cases

The 'bacon kidney' of renal amyloidosis was described by von Rokitansky in 1842. Two years earlier, in *Traité des maladies des reins*, Rayer had recorded renal vein thrombosis, illustrated in his companion Atlas-in-folio in 1837 (Plate 11, Fig. 2). The upper right drawing of Rayer's plate VII shows the left kidney of a young girl 'morte d'une hydropisie générale, avec urine albumineuse'. The kidney is obviously enlarged, and the cortex is described as 'd'un blanc-jaunâtre humide, tirant sur le jaune abricot'. The right kidney (the lower left drawing of Rayer's illustration) is described: 'La teinte anémique et jaune abricot de la substance corticale est très prononçée'. The bilateral renal vein thrombosis is also clearly illustrated. Rayer's second patient was a 57-year-old labourer suffering from bilateral chronic pulmonary tuberculosis. Proteinuria

[1] Received March 23, 1959.

TABLE I

Recorded Cases of Renal Vein Thrombosis in Amyloidosis of the Kidneys

Author	*Date*	*Case number*	*Sex*	*Age (years)*	*Renal vein thrombosis*	*Primary disease and aetiological factors*	*Clinical features*
Gruber . .	1919	..	M	26	Bilateral	Pulmonary tuberculosis	No clinical details
Neu . . .	1922	..	M	32	Bilateral	Endocarditis verrucosa	Chronic 'nephrosis'. Uraemia: non-protein nitrogen 89 mg./100 ml.
Schröder . .	1926	7	M	79	Bilateral	Bronchiectasis	Nephrotic syndrome
Zadek . .	1929	2	M	25	Bilateral	Serofibrinous arthritis	Uraemic acidosis. Alkali reserve 22·6 vol. %
Schauwecker .	1930	2	M	43	Bilateral	Pulmonary tuberculosis	Urinary deposit: leucocytes +++, erythrocytes +, no casts
Siegmund . .	1935	1	M	71	Bilateral	Tuberculous spine	Albuminuria. Died in uraemic coma
		2	F	23	Bilateral	Bone and gland tuberculosis	Albuminuria. Non-protein nitrogen 49·5 mg./100 ml.
		3	M	56	Bilateral	Bronchiectasis	No clinical details
Opsahl . .	1936	2	M	31	Bilateral	Bilateral pulmonary tuberculosis	,, ,,
		3	F	36	Unilateral (left)	Bilateral pulmonary tuberculosis	,, ,,
Heilmeyer and Lipprose	1936	Footnote only			Unilateral	..	,, ,,
Schwartz . .	1938	1	M	'Young'	Bilateral	Not known	,, ,,
Behr . . .	1938	S. 52	M	53	Bilateral	Not known	,, ,,
		S. 205	F	50	Unilateral (right)	Not known	,, ,,
		S. 748	M	22	Unilateral (right)	Not known	,, ,,
		S. 1176	M	30	Unilateral (right)	Not known	,, ,,
Vilk . . .	1940	1	..	34	Bilateral	Fibro-productive tubercle of lungs. Syphilitic periostitis of tibia	Non-protein nitrogen 80 mg./100 ml. Albuminuria. Sp. gr. 1,007–1,015
		2	..	21	Bilateral	Congenital bronchiectasis	Albuminuria. Non-protein nitrogen 360 mg./100 ml. Alkali reserve 33·8 vol. %
		3	..	17	Bilateral	Tertiary syphilis	Albuminuria
		4	..	34	Bilateral. Veins of medulla and pelvis	Fibrotic tuberculosis of lungs	Albuminuria. Urea 292 mg./100 ml.
		5	..	32	Bilateral	Tertiary syphilis	Albuminuria. 'Uraemic pneumonia'
		6	..	24		Fibrotic tuberculosis of lungs and bronchiectasis	Albuminuria. Anuria 2 days
		7	..	24	Bilateral. Fine renal vessels, and partial in main vessels	Fibrotic tuberculosis of lungs and bronchiectasis	Albuminuria. Alkali reserve 19·5 vol. %. Non-protein nitrogen 184 mg./100 ml.
		8	..	57	Bilateral. Early organization	Fibrotic tuberculosis of lungs	Albuminuria. Sp. gr. 1,006–1,011
		9	..	21	Bilateral	Chronic osteomyelitis with fistulae	..
		10	..	58	Bilateral. Early organization	Chronic purulent ulcerative dermatitis of right shin	Albuminuria

		11	..	27	Bilateral. 'Fine' renal veins only	Purulent tuberculosis	Gastritis and enterocolitis
		12	..	13	Bilateral. Organization	Purulent tuberculous lymphadenitis of hilar glands	Alkali reserve 9 vol. %. Non-protein nitrogen 60 mg./100 ml.
		13	..	..	Unilateral	Pneumo-sclerosis (? fibrosis of lungs)	Non-protein nitrogen 100 mg./100 ml. Albuminuria
Frenkel and Groen	1954	2	M	26	Unilateral	Enterocolitis (corticotrophin)	Uraemia
Harrison, Milne, and Steiner	1956	6	M	52	Bilateral	Bilateral pulmonary tuberculosis	Albuminuria 5–8 g./l. Urea 430 mg./100 ml.
		7	M	46	Bilateral	Bilateral pulmonary tuberculosis	Proteinuria 6 g./l.
		8	M	74	Bilateral	Chronic bronchitis	Urea 275 mg./100 ml.
		9	F	18	Bilateral	Old perinephric abscess	Proteinuria 10 g./day
Sinclair and Cruickshank	1956	13	F	68	Bilateral	Rheumatoid arthritis. Congestive cardiac failure. Diarrhoea	Albuminuria
Penfold and Rhys-Lewis	1957	..	M	41	Bilateral	Ankylosing spondylitis	Blood urea 390 mg./100 ml. Heavy albuminuria
Hasson, Berkman, Parker, and Rifkin	1957	6	M	32	Bilateral	Ulcerative colitis	Blood urea 115 mg./100 ml.
Jackson . .	1957	Dr. C. H. C. Toussaint's case	F	About 25	Bilateral	Pulmonary tuberculosis	Terminal uraemia
Chambers, Medd, and Spencer	1958	3	F	52	Unilateral	Nil	Terminal uraemia

and massive oedema occurred five months before death; at necropsy Rayer found bilateral renal vein thrombosis and considerable enlargement of the kidneys. Their yellowish-white colour was noted, and the appearance on section of the left kidney was similar to that in the first case. In the right kidney 'une injection vasculaire modifie la couleur jaunâtre de la substance corticale'. It seems likely that the clinical history and macroscopic findings indicate amyloidosis, and if so, Rayer, in describing renal vein thrombosis for the first time, also provided the earliest record of the association of that condition with amyloid disease of the kidney. Vidal, in 1854, described another case of thrombosis in probable renal amyloidosis, but without microscopical proof. The 'yellowish-white marbled cut surface of the large firm kidneys' is certainly suggestive of amyloidosis.

TABLE II

Summary of Cases

Case No.	*Sex*	*Age (years)*	*Distribution of thrombi*	*Primary disease and possible aetiological factors*	*Evidence of defective renal function*
1	M	57	Unilateral (right). Major tributary veins	Pulmonary tuberculosis	Proteinuria. Terminal oliguria and uraemia
2	F	30	Bilateral and inferior vena cava	Pulmonary tuberculosis	Proteinuria. Terminal oliguria and uraemia
3	F	57	Bilateral. Major tributary veins	Rheumatoid arthritis	Proteinuria. Terminal drowsiness
4	F	28	? Unilateral (one kidney available). Major tributary veins	Pulmonary tuberculosis	Nephrotic syndrome with uraemia
5	M	40	Unilateral (left); partial occlusion of main vein	Probable tuberculous arthritis	Proteinuria. Uraemia with terminal oedema
6	F	34	Bilateral	Pulmonary tuberculosis	Nephrotic syndrome with oliguria and uraemia
7	M	40	Bilateral	Chronic empyema with broncho-pleural fistula following pneumonectomy for adenoma	Proteinuria. Terminal oliguria and uraemia
8	M	24	Unilateral (right). Major tributary veins	Hodgkin's disease	Proteinuria. Terminal oliguria and uraemia
9	F	33	Bilateral	Pulmonary tuberculosis and tuberculous arthritis	Terminal uraemia

An excellent account of 'Lardaceous Disease of the Kidneys' appeared in the second volume of Dickinson's book *On Renal and Urinary Affections*, published in 1877. In the third volume, eight years later, he described the association of renal vein thrombosis and renal amyloidosis. Reference is made to three cases, the first being a Lady Beauchamp, reported by John Hunter. Four months after the opening of an abscess in the region of the hip, she 'succumbed with quick pulse, pains in the right side and irritability of the stomach'. A post-mortem examination was carried out by Hunter, who described the organs, with one exception, as 'natural'. The right kidney was large, hard, and solid, and of a dark red colour. We have now studied sections cut from this kidney, which is an exhibit in the Hunterian collection at the Royal College of Surgeons of England, but our techniques fail to show either morphological or tinctorial evidence of amyloid in this 200-year-old material.

The association of amyloidosis of the kidney and renal vein thrombosis was

familiar to Gaylord and Aschoff, who in 1902 wrote: 'Widespread thrombosis in the veins of the kidney commonly accompanies amyloid degeneration of the organ. An investigation of the vessels with this in mind becomes a matter of routine in amyloid disease of the kidneys.' Yet a review of the literature has revealed only 39 cases of renal vein thrombosis in patients with amyloidosis of the kidneys (Table I), 13 of these cases being recorded by Vilk (1940) from a series of 249 necropsies on subjects with amyloid disease. The association seems, in Dickinson's phrase, to have dropped out of notice. These past studies have revealed no convincing explanation for the association of thrombosis with amyloidosis. The present paper records nine cases of this association (summarized in Table II); the pathogenetic factors, clinical presentation, and therapeutic implications are discussed.

Case Reports

Case 1. A man of 57 years, who had received prolonged drug therapy for extensive pulmonary tuberculosis, became suddenly ill with vomiting and diarrhoea in October 1956. Proteinuria was discovered, and he died two months later in oliguric renal failure with terminal stupor.

Post-mortem findings. Bilateral fibrocaseous tuberculosis of the lungs, and extensive amyloid infiltration of the kidneys, liver, spleen, and adrenals were demonstrated. Both main renal veins were patent, but tributary veins on the right side were filled with thrombus down to arcuate level. Capillary thrombi were present in a few glomeruli.

Case 2. A 30-year-old woman, with a long history of uncontrolled pulmonary tuberculosis, developed a severe attack of vomiting, followed by oliguria, in November 1956. Examination of the urine showed protein and pus cells, but no tubercle bacilli. Proteinuria was known to have been present for at least 18 months. Peripheral oedema was associated with a low serum-albumin level. The patient died two months later with persistent oliguria and uraemia.

Post-mortem findings. Fibrocaseous pulmonary tuberculosis and amyloid change in the kidneys, liver, and spleen were demonstrated. The main renal veins were completely occluded by thrombi, and on each side thrombosis extended to arcuate level. There was clot in the inferior vena cava as far as the intrahepatic portion.

Case 3. A 57-year-old woman, with a long history of severe rheumatoid arthritis, was admitted to hospital in October 1956 after the discovery of hepatomegaly, splenomegaly, and proteinuria. In the past she had received a five-year course of treatment with cortisone. Six months later she became suddenly ill, and died in a stuporose condition within two weeks.

Post-mortem findings. Widespread rheumatoid deformities of the joints and amyloidosis of the kidneys and liver were demonstrated. The main renal veins were patent, but thrombi were seen on both sides in the interlobar, arcuate, and medullary veins, and in the capillaries of the glomeruli and intertubular plexus.

Case 4. A 28-year-old woman, who gave a long history of pulmonary tuberculosis, developed oedema of the ankles, vomiting, and oliguria in June 1953.

Proteinuria was heavy, and the blood urea was 203 mg. per 100 ml. Three days later she lapsed into coma and died.

Post-mortem findings. Fibrocaseous pulmonary tuberculosis and amyloid deposition in the kidneys, spleen, and liver were demonstrated. Only one kidney was examined, in retrospect, for the presence of thrombi. Thrombosis was found in the major tributaries, and extended to arcuate level, with a few capillary thrombi in the glomeruli.

Case 5. A man of 40 years, with long-standing ankylosis of the left hip, was found to have proteinuria and increased blood urea in August 1957. Five weeks after repair of a perforated duodenal ulcer he developed abdominal pain, vomiting, and oedema of the ankles. Uraemic stupor preceded his death three days later.

Post-mortem findings. Bilateral apical pulmonary fibrosis, and amyloidosis of the kidneys, liver, and spleen were demonstrated. The affected hip joint was not examined. Thrombi were present in the left main renal vein and tributaries. No arcuate veins were affected, but a few capillary thrombi were seen.

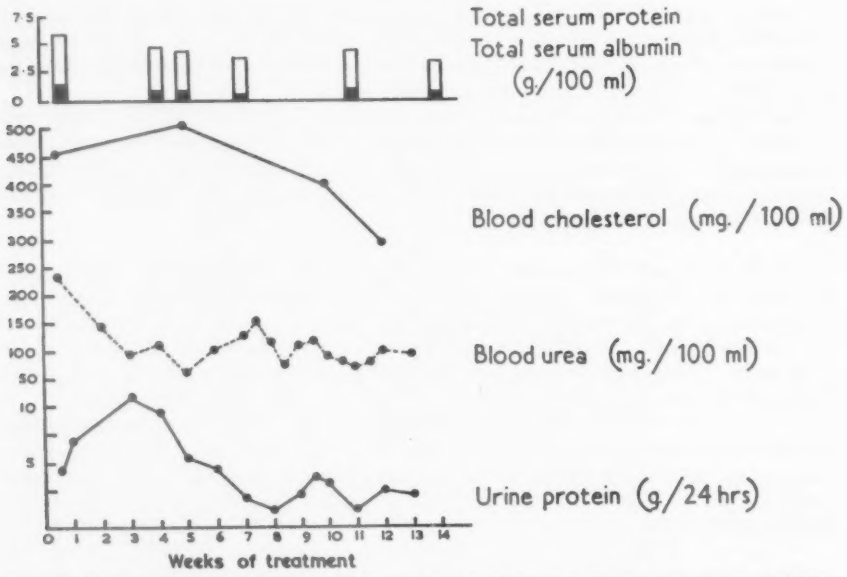

FIG. 1. Progress during treatment with anticoagulant drugs in Case 6 (a woman aged 34).

Case 6. A 34-year-old woman, who had had pulmonary tuberculosis for 14 years, became oliguric, with azotaemia, after a thoracoplasty in 1956. Enlargement of the liver and proteinuria had been observed in 1953. She recovered from this episode, but four weeks later oliguria recurred, with peripheral oedema, the blood urea increasing to 230 mg. per 100 ml. Electrophoresis of the serum proteins showed the pattern characteristic of the nephrotic syndrome. A clinical diagnosis of amyloidosis was confirmed by Congo red dye retention, and the possible complication of renal venous thrombosis led to a trial of anticoagulant drugs. The changes in renal function during the ensuing three months of treatment are charted in Fig. 1, and included a fall in the blood-urea and blood-cholesterol levels, with a marked decrease in proteinuria. Four months

later the patient's general condition deteriorated, and she died in a cachectic state.

Post-mortem findings. Bilateral pulmonary tuberculosis and amyloidosis of the kidneys, liver, spleen, and adrenals were demonstrated. Thrombi were present in the main renal veins and larger tributaries on both sides.

Case 7. A man of 40 years, with a long-standing right-sided empyema, developed vomiting and malaise in July 1957. The urine contained protein, and there was azotaemia, the blood urea increasing rapidly to 590 mg. per 100 ml. during the next few weeks. Despite a clinical diagnosis of renal vein thrombosis secondary to amyloidosis, treatment with anticoagulant drugs was not given, because of a severe bleeding tendency, and for the same reason haemodialysis was not attempted. Progressive drowsiness preceded the patient's death in coma one week later.

Post-mortem findings. Amyloidosis of the kidneys, spleen, and liver was demonstrated. Thrombi were present in the main renal veins and in their tributaries to arcuate level.

Case 8. A man of 24 years, in whom a diagnosis of Hodgkin's disease had been made in 1944, was first found to have enlargement of the liver and spleen in 1953. In 1956 he developed proteinuria, and six months later deterioration in his condition led to treatment with nitrogen mustard. Vomiting, oliguria, and severe azotaemia followed. Haemodialysis with an artificial kidney produced no clinical improvement, despite a fall in the blood-urea level, and he died on the following day.

Post-mortem findings. Widespread involvement of lymph-nodes by Hodgkin's disease was confirmed, and amyloidosis of the kidneys, liver, and spleen was demonstrated. The main renal veins were patent, but thrombosis was seen in the interlobar veins and glomerular capillaries on the right side.

Case 9. A 33-year-old woman, as a result of food poisoning, had vomiting and diarrhoea, which persisted until her death three weeks later in uraemic stupor. Ankylosis of the left hip, with numerous well-healed sinus scars, was noted.

Post-mortem findings. Bilateral fibrocaseous tuberculosis of the lungs and amyloidosis of the kidneys, liver, spleen, intestines, adrenals, ovaries, uterus, and myocardium were demonstrated. Thrombi were present in both main renal veins and in their tributary veins to arcuate level. Thrombosis of glomerular capillaries was also present.

Distribution of Thrombi

The anatomical result of occlusion of the renal venous system is varied, and in some cases seems to be the climax of a steady progression of thrombotic incidents within the kidney. To test this hypothesis, a thorough survey has been made of the distribution and histological character of the thrombi in the kidneys of the nine cases of renal venous thrombosis in association with renal amyloidosis, and the findings are summarized in Table III. In some instances only one or two blocks of the kidneys were available, and in one instance (Case 4) only one kidney was available for study.

Discussion

Amyloid 'nephrosis'. Thrombosis of the renal venous system is an important, and often terminal, complication of amyloidosis of the kidneys. In most recorded cases the amyloid process has been of the 'secondary' type known to follow

TABLE III

Distribution of Venous Thrombi

Case No.	*Renal veins*	*Major tributary veins*	*Small veins (arcuate and smaller)*	*Capillaries*	*Organization of venous thrombi*
1	None	All thrombotic in one kidney	One arcuate vein	Few in glomeruli and in intertubular plexus. Multiple in some glomeruli. Thrombi in capillaries of perinephric fat	Variable: early in larger veins; advanced in smaller veins
2	Bilateral, with involvement of vena cava	Bilateral. Old thrombus throughout	Many arcuate veins	None	Advanced organization and calcification
3	None	Bilateral. Recent thrombus throughout	A few arcuate veins and medullary venules	Numerous in glomeruli and intertubular plexus	No evidence of organization
4	*(Only one kidney available)* None	Recent thrombus in two pelvic veins and their major tributaries	One arcuate vein. Few medullary venules	Small numbers in glomeruli and in intertubular plexus	No organization of large thrombi. Endothelialization and advanced organization of arcuate thrombus
5	Unilateral (left). Occlusion incomplete	Unilateral	None	Few in glomeruli	Very early organization in renal vein. Advanced organization with addition of fresh fibrin in major tributaries
6	Bilateral	Bilateral	One interlobular vein	None	Variable in main trunk. Parts show advanced organization, but on the surface there is recent fibrin. Thrombus in interlobular veins is organized and calcified
7	Bilateral	Bilateral	Arcuate and medullary venules	One glomerulus	One of the venular thrombi is partly organized
8	None	Unilateral	None	Numerous in glomeruli	Organization of periphery of thrombus in large veins
9	Bilateral	Bilateral	Several arcuate veins. Numerous in medullary venules	Numerous in glomeruli	Organization in arcuate and interlobar veins

such conditions as chronic pulmonary infections, myelomatosis, rheumatoid arthritis, osteomyelitis, Hodgkin's disease, and more rarely chronic ulcerative colitis. Although only one example of renal venous thrombosis in association with primary amyloidosis has been reported (Chambers, Medd, and Spencer, 1958) it has been shown that renal involvement occurs in about 35 per cent. of cases of primary amyloidosis (Symmers, 1956), and it is unlikely that this group is exempt from the hazard of venous thrombosis. Of the present series of nine cases of histologically proven renal amyloidosis, all were of secondary type. In five the apparent cause was long-standing pulmonary tuberculosis, complicated in one instance by an additional tuberculous arthritis with chronic sinus formation. Rheumatoid arthritis, Hodgkin's disease, chronic empyema, and a

presumed tuberculous arthritis, were each responsible for one of the remaining four cases (Table II).

The basic mechanism for the production of amyloidosis is unknown. A modern view is that the characteristic morphological findings result from a disturbance of antibody formation, which in turn results in an excess of circulating antigen (Perāsalo, 1954). It is particularly interesting, therefore, that the amount and rate of amyloid deposition induced by any of the usual experimental methods can be increased by the concurrent administration of corticotrophin or cortisone (Latvalahti, 1953; Teilum, 1952), which themselves are known to depress antibody formation (Fagraeus, 1952). The first clinical evidence to suggest an amyloid-producing action on the part of cortisone was given by West and Newns (1952), who described a 29-year-old patient with rheumatoid arthritis treated with 75 mg. of cortisone daily for a year. A biopsy before treatment showed normal liver, but at necropsy, one year later, it was estimated that 85 per cent. of the liver consisted of amyloid substance. The significance of these findings may be lessened by the fact that for nine months the patient had also received calcium caseinate, a substance known to be effective in the experimental production of amyloidosis (Kuczynski, 1923). Deposition of amyloid following the use of corticotrophin in the treatment of rheumatoid arthritis in one case, and of 'purulent inflammation of the ileum and colon' in another, was noted by Frenkel and Groen (1954) in the spleen, liver, kidneys, and adrenals; the authors commented on the rapidity and amount of this deposition, and advised against corticotrophin or cortisone therapy if amyloidosis is already present. The same conclusion was reached by Bickel and Lasserne (1956) after their use of steroid therapy in the hope of increasing the penetration of antituberculous drugs. Perhaps the most suggestive clinical evidence is the report of Wegelius (1956). He found amyloidosis of the kidneys, adrenals, and spleen in a case of disseminated lupus erythematosus of six years' duration, treated with corticotrophin and cortisone. Albuminuria was already gross before steroid therapy was started, but a lymphocytopenia (a common concomitant of amyloidosis (Perāsalo, Kuusisto, and Halonen, 1950)) developed in the course of treatment. On the grounds that amyloidosis had never before been reported in association with disseminated lupus erythematosus, Wegelius suggested that the steroid therapy was to blame. Cortisone was given to three patients of the present series (Cases 1, 2, and 3) for varying lengths of time, and, although our material does not provide any valid confirmation of the view that adrenosteroid therapy can cause or intensify secondary amyloid disease, such a therapeutic hazard, particularly in view of the possible thrombotic complications, demands urgent further investigation.

Renal venous thrombosis. 1. *The dehydration factor.* Renal vein thrombosis in an infant who had died of cholera was reported in 1850 by Bednar, and eight years later Beckmann published 10 cases of renal vein thrombosis in children. Since then many such reports have appeared, and with increasing understanding it is now clear that the thrombosis was precipitated not by any specific type of infection, but by the degree of dehydration. The adult with amyloid disease

shares the infant's risk in the presence of dehydration; indeed diarrhoea, with or without vomiting, occurred in nine of Vilk's (1940) 13 adult patients with renal vein thrombosis with renal amyloidosis, and in four of our own cases. The main difference between renal venous thrombosis in adults and the corresponding lesion in infants is the effect of the venous occlusion on the parenchyma of the kidney. This is probably due to the differing tempo of the process in the two age groups. In adults the thrombotic process seems to be of slower evolution, with more time available for the development of collateral drainage. This influence of the speed of venous occlusion has been noted by Morison (1945) and by Bell (1950), and has been demonstrated experimentally (Rowntree, Fitz, and Geraghty, 1913; Harrington, 1921; Behr, 1938). In infants dehydration appears to be the dominant factor; in adults it is probably no more than one precipitating factor in an already prepared field.

2. *The fibrinogen factor.* When patients with amyloid disease have their blood cross-matched, there is frequently an extreme degree of rouleaux formation, possibly in part related to the greatly raised plasma-fibrinogen level so commonly seen in cases of secondary amyloid disease (Johansson, 1955). In the experimental production of amyloid by the induction of inflammation there is usually an increase in the plasma fibrinogen, but if this fails to occur there is apparently little likelihood that amyloid substance will be produced (Fendel and Gerok, 1955). It appears, therefore, that a rise in fibrinogen level may be a significant part of the mechanism whereby a primary disease is followed by the deposition of amyloid, and, once amyloid disease is established, an elevated plasma-fibrinogen level may be maintained or begin to rise again with the onset of the nephrotic syndrome.

3. *The thrombo-fibrinolytic factor.* The distribution of the thrombi in the kidneys of our patients is surprising, and explanation is difficult. First, the estimation of the age of thrombi in histological sections lacks any certain criteria. Secondly, we have no histological means of recognizing current fibrinolytic activity; and, thirdly, the development and propagation of thrombus within the kidney is probably influenced by the peculiar vascular arrangement, in which the sequence of the coiled glomerular capillaries, subject to perpetual concentration of their contents, is followed by a system of long narrow venous sinuses from which the rediluted blood is only distally gathered into normal-looking veins.

Thrombosis within glomerular capillaries was seen in seven of the nine cases, and most prominently in Cases 3 and 8. These capillary thrombi should perhaps be regarded as less permanent than they appear, if the fibrinolytic mechanism is as potent as is now suggested. This fibrinolysis has been known for a long time (Dastre, 1893), but recent researches (Macfarlane and Biggs, 1946; Macfarlane and Pilling, 1946; Astrup, 1956) have proved it to be highly active. Fearnley and Ferguson (1957) described it as a 'normal property of the blood, enhanced rather than induced by various kinds of stress'. The activity is aided by mechanical factors within the vascular system, as was demonstrated experimentally by Rabin, Thomas, Lee, Konikov, and Scott (1957), who directly

observed the fate of clot particles in the central artery of the rabbit's ear. Even when an embolus plugged a vessel, it was not fixed, but was swept back and forth. During movement pieces of clot were constantly separated from the mass and swept further down the vessel, where the process was repeated until fragments became small enough to clear the capillaries. Most emboli disappeared within an hour. A comparable disappearance of clot has been seen by one of us (H. M. C.) in rabbits' kidneys, in which large numbers of thrombi deposited in the smaller arteries and capillaries by intra-aortic injection of thrombin were completely removed within six hours. The mechanical factor concerned in the experiments of Rabin and his colleagues is probably not relevant in the quieter backwaters of the intertubular sinuses; but we may presume that the small thrombi, whether few or, as in Cases 3 and 8, very numerous, are continually subject to fibrinolytic activity. In the large veins the greater thrombus, by virtue of its mere mass, is presumably less susceptible to the normal fibrinolytic activity and thus may persist, as in Cases 2 and 6, the small originating thrombi having in the meantime been dissolved.

4. *The propagation of thrombus in the venous system of the kidney.* When factors favouring coagulation are predominant, or when fibrinolysis is less effective, thrombosis may occur within the glomerular capillaries (Plate 12, Figs. 3 and 4). To reveal these thrombi in histological sections with any certainty demands adequate fixation, preferably in solutions free of chromates, and a staining method highly specific for fibrin. Study of the sections from our material suggests that propagation occurred along a few of the venules and smaller veins to reach the arcuate and interlobar veins (Plate 13, Figs. 5 and 6) and eventually the main trunk. In the absence of caval or cardiac obstruction, or neoplastic involvement, the occurrence of thrombus in the main renal vein is rare, as it is in any other viscus under comparable conditions. The fact that it can occur there may well be due to the long stagnant plexus (of the intertubular venules) that lies distal to the capillary bed in which we believe the primary thrombosis occurs.

The thrombi in the main renal veins were regarded by Schulman, Dreizin, and Rommer (1950) as being more recent than those demonstrated in the smaller venous radicles of their patient. A similar difference between the extent of organization of the thrombi in the main renal veins and that in the intrarenal venous radicles was seen by Hasson, Berkman, Parker, and Rifkin (1957) in two of their six cases, but in two others the thrombi were completely organized and recanalized. These authors hesitated to estimate or to compare the age of thrombi in vessels of differing size, on the grounds that those of greater bulk will be more slowly organized from their relatively smaller endothelial surfaces. Whether or not we can infer anything from the degree of organization, at least the distribution of the thrombi may be of significance; thus thrombosis did not extend beyond the interlobar venous level in Cases 4 and 11 of Vilk (1940), in Case 6 of Harrison, Milne, and Steiner (1956), or in our Cases 3, 4, and 8; in two patients (Cases 7 and 8 of Harrison, Milne, and Steiner) thrombi extended for a few millimetres into the main venous channels from the interlobar veins; but

thrombosis of the main renal veins without involvement of the tributary veins has not been seen. Propagation of the thrombotic process appears to be in the direction of the blood-stream.

Clinical Presentation, Diagnosis, and Treatment

The localization of renal venous thrombi may influence the nature of the disturbance of kidney function. Two possible modes of clinical presentation of renal vein thrombosis, from any cause, have been recognized: (1) the sudden onset of a nephrotic syndrome; (2) a rapid deterioration of renal function with oliguria and uraemia (Harrison, Milne, and Steiner, 1956). These authors, in their series of 11 cases, recorded the former mode of onset in three patients and the latter in six. Of the other two patients, one had malignant hypertension, and the other tumour-thrombosis secondary to hypernephroma. In four patients there was an underlying renal amyloidosis; three of these presented a sudden deterioration of renal function with oliguria, leading to death in uraemia within one month, while the fourth was already severely uraemic when first seen. Where thrombosis is associated with pre-existing parenchymal disease, such as amyloidosis, the smallest vessels are affected (Plate 12, Figs. 3 and 4), and the development of an uncomplicated nephrotic syndrome does not occur. Of the present series of nine cases, six showed a rapid deterioration of renal function with oliguria, though in four of them precise clinical details were not available. Two presented a nephrotic syndrome which was, however, in both instances rapidly followed by severe oliguria and terminal uraemia. The remaining patient was found to be uraemic after a three-week period of vomiting, and died within 48 hours of admission to hospital.

Confirmation of a suspected diagnosis of renal vein thrombosis may be obtained by venography only if the main vessels are involved. The two routes available are the inferior, via a saphenous vein, and the superior, by a cardiac catheter inserted into an antecubital vein. Where, however, renal disease is known to exist, as in the case of amyloidosis, such confirmation is rarely indicated, may be dangerous, and is often unhelpful if the intrarenal vessels alone are occluded by thrombus. Where the main veins are affected, useful information may be obtained from the presence on the lower abdominal wall of venous collateral vessels, in which the upward flow of blood indicates the extension of thrombosis to the inferior vena cava.

The importance of clinical recognition of the development of renal vein thrombosis, from any cause, lies in the therapeutic possibilities. Treatment with anticoagulant drugs has been recommended by several authors, but the number of treated patients recorded is small. No treated case of thrombosis secondary to renal amyloidosis has been described. There is suggestive evidence from the case of Pollak, Kark, Pirani, Shafter, and Muehrcke (1956) that heparin may be of value in the treatment of renal venous thrombosis not associated with amyloidosis, but in the case described by Cruchaud (1956) heparin was discontinued after a few days on account of increased haematuria. This patient died after

three months, and at autopsy was found to have thrombosis of tributary and main renal veins on both sides; thrombosis had spread to the inferior vena cava; there was no antecedent renal disease.

Anticoagulant therapy has been recommended in cases of known renal amyloidosis in which there is sudden oliguria and uraemia (Harrison, Milne, and Steiner, 1956); these authors stated that the prognosis is better when the main renal veins, rather than the smaller intrarenal tributaries, are involved. In Case 6 of the present series, in which both tributary and main renal veins were occluded by thrombus, definite temporary improvement in renal function was achieved, as shown by the decreased urinary protein output and blood urea and the fall in the blood-cholesterol level (Fig. 1). In the second patient, in whom the diagnosis was made during life (Case 7), the presence of a severe haemorrhagic diathesis, presumed to be due to uraemia, was considered a contraindication to the use of anticoagulant drugs. In addition, we have had further experience of the use of anticoagulant drugs in renal vein thrombosis, due in this instance to presumed tumour-thrombosis of the contralateral renal vein following nephrectomy for a hypernephroma in a 62-year-old man. Forty-eight hours after operation the patient developed severe oliguria, proteinuria, and oedema of the lower limbs. The presence of collateral veins in the left flank with upward blood-flow led to a diagnosis of obstruction of both the inferior vena cava and the left renal vein. Treatment with intravenous heparin was started, and 10 days later the patient had a satisfactory diuresis; the blood urea, which had risen to 300 mg. per 100 ml., gradually returned to normal. Oedema of the lower limbs resolved. Attempted venography by the inferior route failed owing to extensive occlusion of the iliac veins.

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Summary

A review of the literature relating to renal venous thrombosis associated with amyloidosis of the kidney is given, and nine further cases are described.

Thrombosis following an episode of dehydration, in patients with glomerular changes due to amyloid deposition, may be related to a regional deficiency of fibrinolysis; and consideration of these factors, along with our histological findings, suggests that the primary origin of the thrombi is at capillary level. The fact that this thrombotic process occurs in the kidney rather than elsewhere may be related to its unique vascular anatomy.

The clinical modes of presentation are discussed. It is suggested that treatment with anticoagulant drugs should be considered in all cases of renal venous thrombosis, including those associated with parenchymal disease such as amyloidosis, unless a severe bleeding tendency is recognized or haemorrhage occurs during the course of such therapy. The purpose of treatment is to allow time for the development of an effective collateral venous drainage system and, to this end, haemodialysis may also be applied.

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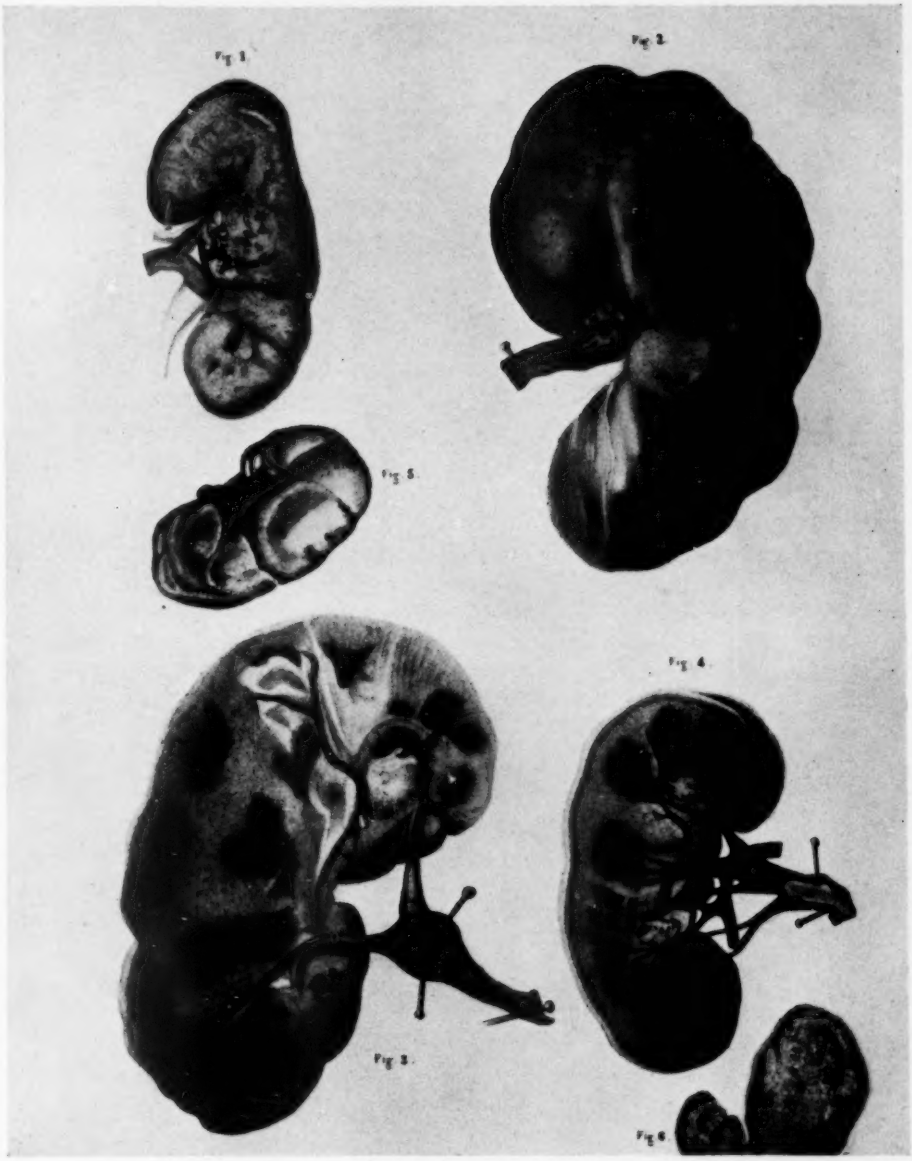

FIG. 2. Plate VII of Rayer's Atlas. The upper right (Fig. 2) and lower left (Fig. 3) drawings show the left and right kidneys of the girl who died with generalized oedema and albuminous urine. The bilateral renal vein thrombosis is well illustrated

The clinical modes of presentation are discussed. It is suggested that treatment with anticoagulant drugs should be considered in all cases of renal venous thrombosis, including those associated with parenchymal disease such as amyloidosis, unless a severe bleeding tendency is recognized or haemorrhage occurs during the course of such therapy. The purpose of treatment is to allow time for the development of an effective collateral venous drainage system and, to this end, haemodialysis may also be applied.

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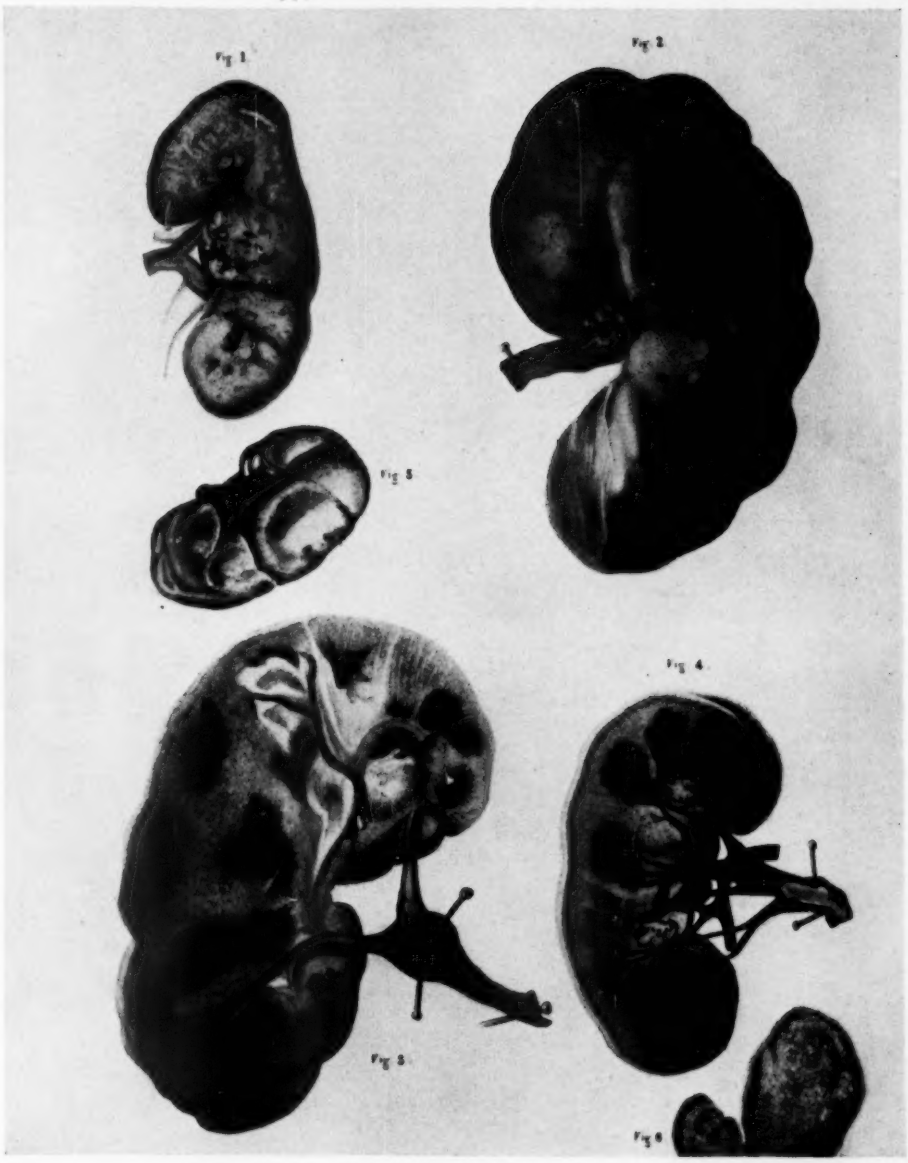

FIG. 2. Plate VII of Rayer's Atlas. The upper right (Fig. 2) and lower left (Fig. 3) drawings show the left and right kidneys of the girl who died with generalized oedema and albuminous urine. The bilateral renal vein thrombosis is well illustrated

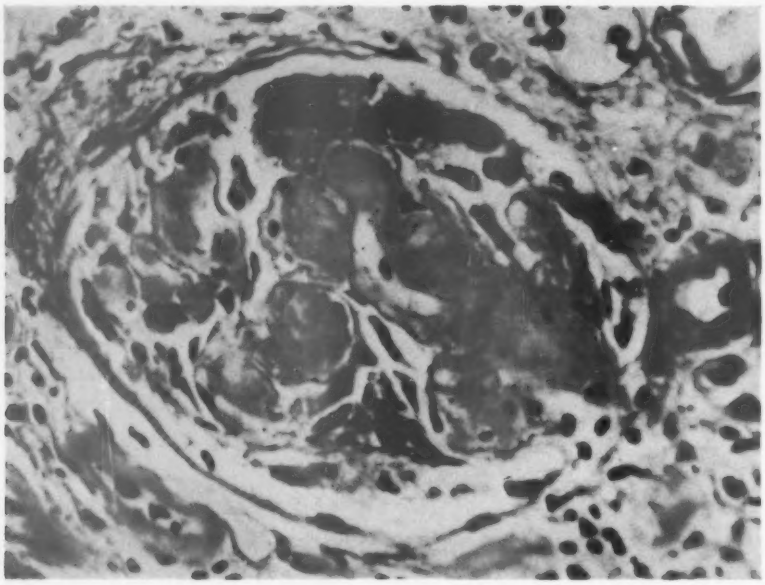

FIG. 3

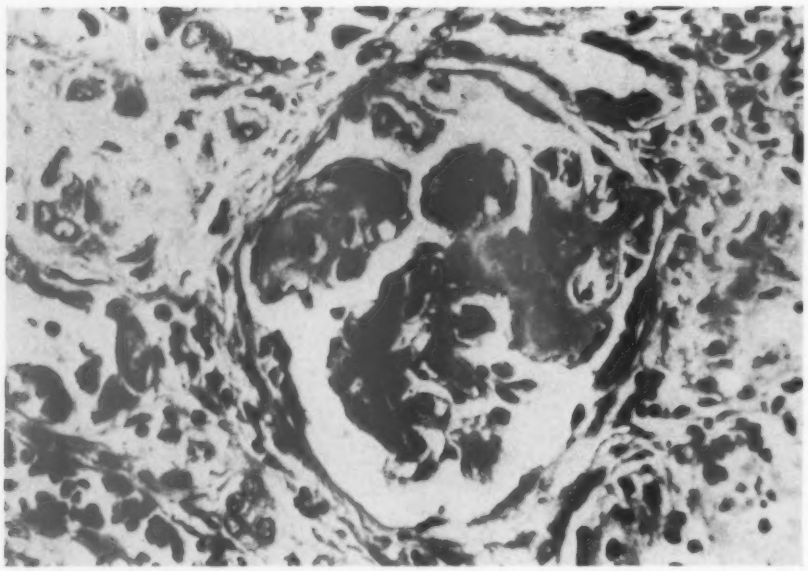

FIG. 4

FIGS. 3 and 4. Case 1. Sections of kidney to show obliteration of capillaries in amyloid glomeruli by masses of thrombus (black). Stain: picro-Mallory V. Minus red filter; Fig. 3 × 280; Fig. 4 × 420

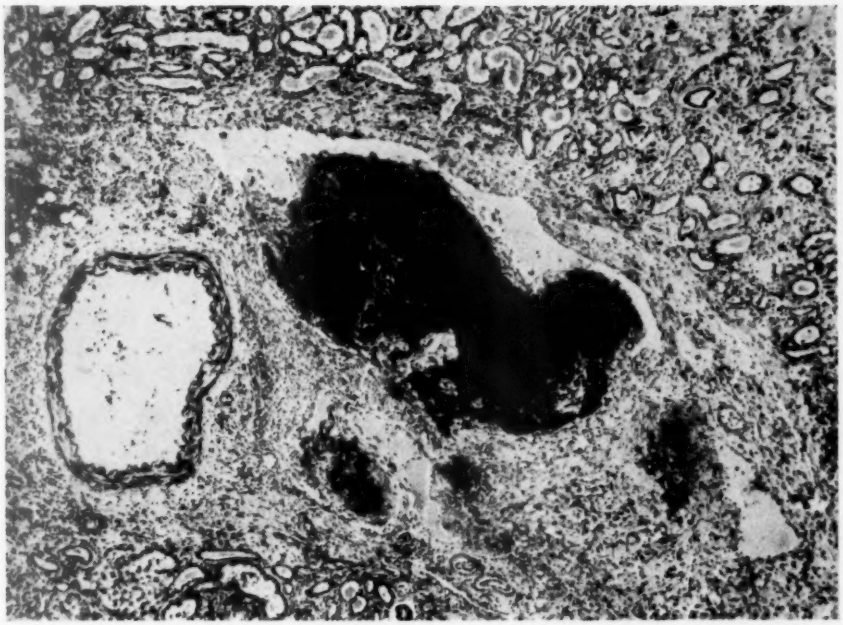

FIG. 5. Case 9. An arcuate vein with thrombus showing evidence of organization. Stain: modified phloxin tartrazine. Minus red filter; ×25

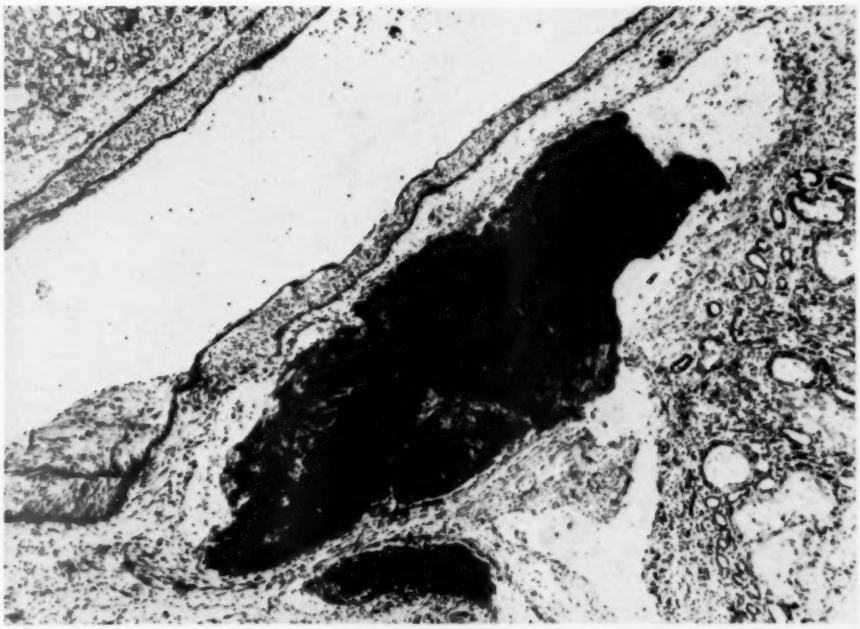

FIG. 6. Case 9. An interlobar vein containing thrombus is cut spiralling round its accompanying artery. Stain: modified phloxin tartrazine. Minus red filter; ×25

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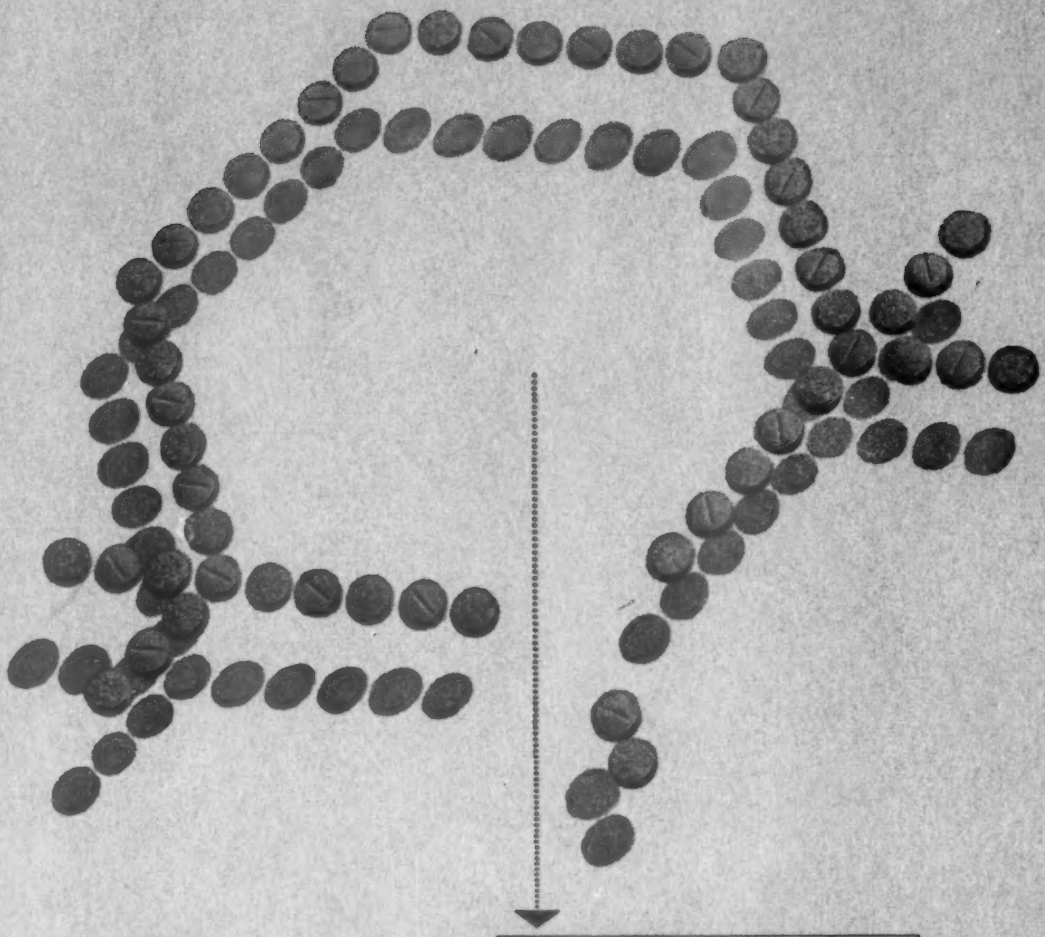

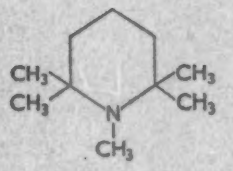

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